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PULMONARY EMBOLISM AND HEART DISEASE.

A REVIEW OF 20 YEARS OF PERSONAL EXPERIENCE.*

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PULMONARY embolism and infarction, recognized as a cause of dyspnea, blood spitting, and rapid death since the time of Theophilus Bonetus[1] more than 250 years ago, are conditions of such importance because of their frequency and clinical effect, that it is surprising that the medical profession has been so slow in paying adequate attention to them. This statement applies especially to practitioners of general medicine and of internal medicine; surgeons have long been concerned quite naturally about the complication of pulmonary embolism postoperatively, and pathologists and roentgenologists have become increasingly interested of late in the study of infarcts of the lung.[2–4] But so far as I know there have not yet been assembled in concise form certain medical aspects of the problem, particularly as encountered by one like myself dealing primarily with heart disease. I have been confronted time and again in the last 10 years by various angles of the association of pulmonary embolism with heart disease, including postmortem observation, not taught me in medical school or in my early hospital experience.

I have kept a file of initial diagnoses in my private patients since my start with them 20 years ago, and these I have looked over to ascertain the development of my own recognition of pulmonary embolism and infarction, first, as conditions simulating heart disease and, second, as complications of heart disease. I make no claim to more rapid progress in this respect than the next man; doubtless I have lagged behind some, but it is possible that my experience may be helpful to others. The long-time observations of a single observer are often quite useful. I am recording now only my initial diagnoses, quite a few of which have been checked by

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autopsy. At least as many more of the cases developed pulmonary embolism or infarction after I had first seen them, some that could be found only at autopsy. I am not including in this analysis the cases that I have seen in the open hospital wards, but those patients have demonstrated much the same points.

I shall summarize my experiences by recounting first, the increasing frequency with which I have recognized the condition; second, the possible confusion in diagnosis; third, the frequency with which pulmonary embolism complicates heart disease; and fourth, helpful signs of its presence.

We were taught in medical school to look for pulmonary embolism in cases of serious and sometimes obscure postoperative complications, but I still remember my surprise 25 years ago in the discovery postmortem in London in one of Thomas Lewis' patients with congestive heart failure of a massive hemorrhagic infarct of the lung as a cause of jaundice.

In the ten years from 1920 to 1930, I made an initial diagnosis of pulmonary embolism simulating or complicating heart disease in only 9 cases definitely and in only 7 cases questionably among 4000 patients; in 3350 patients in the last decade, on the other hand, the number of definite diagnoses has increased from 9 to 66 and of questionable diagnoses from 7 to 39. My type of practice has not changed; these cases have all been cardiac in nature or thought to have been cardiac when referred to me.

Of the total 75 definite cases, only 29 were diagnosed in the first 16 of the 20 years among 6000 patients, while the balance of 46 cases were noted among 1350 in the last 4 years. I am sure, in retrospect, from my case records and from review of the autopsy reports at the Massachusetts General Hospital that there has not been such an amazing increase in pulmonary embolism and infarction rather suddenly in the last 5 to 10 years, as these figures would suggest, but that a large part at least of the increase has been due to our better recognition of the condition, especially in the clinic, and also even in the autopsy room, though to a lesser degree. I find that I diagnosed pneumonia, bronchial or atypical lobar, and also sometimes congestive failure between 1920 and 1930 in patients who today would be quite clearly recognized as having pulmonary infarction. Even the pathologists believe that they on occasion were calling some infarcts pneumonia, as were the roentgenologists. In our clinic at the moment, on the other hand, there is, in our enthusiasm, probably more danger of overdiagnosis of pulmonary embolism than of its underdiagnosis.

Of the total 75 definite cases referred to above, 28 simulated and 47 complicated heart disease. The acute cor pulmonale was first diagnosed in October, 1932,[7–9] and I have since seen 13 other private patients who I thought deserved this designation. Of the 75 definite cases, 42 were males and 33 were females. The age

range was from 15 to 87, with the majority in the 50's and 60's. The cardiac diagnoses in those cases with definite heart disease in which pulmonary embolism or infarction occurred as a complication were coronary disease, mostly with myocardial infarction and with or without hypertension, in 26, rheumatic heart disease, mostly with mitral stenosis and auricular fibrillation in 15, hypertensive heart disease in 2, patent ductus arteriosus with subacute bacterial endocarditis in 1, and cardiac enlargement with no other evident abnormality than chronic auricular fibrillation or flutter in 3 cases (2 of fibrillation and 1 of flutter). Of the 47 cases, 29 were in congestive failure and 15 showed auricular fibrillation. Peripheral phlebitis was evident in only a few cases, but it is probable that the majority might have shown such a lesion if we could have explored the veins; at least, that is the lesson to be derived from the postmortem findings at the Massachusetts General Hospital where some 70% of the medical pulmonary embolism cases have phlebitis that gives little or no clinical evidence of its presence. However, the frequency with which large hearts in failure with auricular fibrillation were present in my group allows either the heart itself or the veins or both to be incriminated as the source of the emboli to the lungs; the great preponderance of pulmonary emboli probably comes from the leg and pelvic veins. Rare cases of pulmonary infarction may have originated from pulmonary thrombosis *in situ;* it is also probable that a small embolus may be backed up by thrombosis after it has blocked a vessel.

There are four remaining points which I would like to emphasize. The first is the frequency with which pulmonary embolism and infarction may occur in medical as well as in surgical cases: in a series of 370 cases of pulmonary embolism and infarction analyzed at autopsy at the Massachusetts General Hospital by Hampton and Castleman,[3] 40% were postoperative with 58% infarcts, 30% were cardiac *with 90% infarcts,* and 30% were non-cardiac medical with 62% infarcts. The second point is that some of the medical cases without chronic heart disease simulate cases of heart disease itself by the development of pulmonary artery and right ventricular dilatation, sometimes with engorgement of the neck veins and a characteristic electrocardiogram. This combination of findings we have labelled the acute cor pulmonale,[7–9] *but it is, of course, present in only a small minority of cases of pulmonary embolism,* for there must be a large enough obstruction to the pulmonary circulation to overload the heart in the first place but not large enough to cause early death in a state of shock. The chief importance in the recognition of the acute cor pulmonale is to differentiate it from acute coronary thrombosis with myocardial infarction. The transition of acute cor pulmonale to a chronic cor pulmonale is quite possible,[2] but we have not yet studied it ourselves. One other way in which pulmonary infarction can simulate heart disease or rather heart

failure is to produce signs, especially dullness and râles at one or both lung bases, which are taken for pulmonary edema with or without a little hydrothorax, in a patient who already has heart disease but is not actually in failure.*

The third point concerns the ease and frequency with which pulmonary embolism and infarction complicating heart disease can be overlooked, especially if there is already congestive heart failure behind which, at the lung bases for example, the infarcts may hide.[6] Clues may be found, such as the periodic occurrence of unexplained attacks of faintness, prostration, dyspnea, or *tachycardia* (especially), followed by fever[5] and leukocytosis, or by an increase of fever, if such is already present due to a hidden phlebitis or perhaps in slight to moderate degree from the congestive failure itself; discomfort on breathing and an obscure slight jaundice may also be clues. There may or may not be any chest pain, or cough, or blood spitting. Emboli are usually multiple and recurrent and hence punctuate the chart rather characteristically to explain what used to be called bronchopneumonia, although it is true that pneumonia may complicate pulmonary infarction and be found with it at autopsy. It is of interest that of 50 cardiac patients with congestive failure examined postmortem, reported recently by Dr. Kinsey and myself,[5] every single one showed some complication which may well have been the proverbial last straw; pulmonary infarction headed the list with 24 cases, bronchopneumonia was next with 20, and acute rheumatic infection and acute coronary thrombosis tied for third with 8 each; there were multiple complications in several cases.

Finally, the fourth point is this: in a cardiac patient with congestive failure who fails to respond as he should to treatment, it is important to bear in mind the possibility not only of pulmonary infection or rheumatic fever, but also of the more common complication, namely, pulmonary infarction.

Summary. 1. Pulmonary embolism has surprisingly failed to attract the interest and attention it has deserved from general practitioners and those working primarily in the field of internal medicine, in contrast to its long-standing recognition by surgeons and obstetricians as a serious complication after operation, accident, or childbirth. It needs emphasis as a medical disease because of its frequency and importance in non-surgical and non-obstetrical cases.

2. My own experience is probably typical of that of many who have only in recent years begun to be on the lookout for pulmonary

* It is of additional interest and importance that pulmonary embolism alone may on occasion precipitate pulmonary edema or asthmatic breathing, and so may simulate acute left ventricular failure; especially does this happen if mitral stenosis or some strain involving the left ventricle (hypertension, aortic valve disease, or myocardial infarction) is already present. It is quite possible that sometimes in the presence of limited myocardial reserve there may be a two-fold reason for pulmonary edema or asthmatic breathing, namely the pulmonary embolism itself and left ventricular failure.

embolism. In 10 years from 1920 to 1930 I made an initial diagnosis of this condition either simulating or complicating heart disease in only 9 cases definitely and in only 7 cases questionably among 4000 patients; while in the last decade among somewhat fewer patients (3350) there were nearly 7 times as many such cases diagnosed (66 definite and 39 questionable).

3. About one-third of my cases simulated and the remainder complicated heart disease. Of the former (28 in number) one-half (14) showed the signs of the acute cor pulmonale described by McGinn and myself in 1935, including characteristic electrocardiographic abnormalities. In most cases pulmonary embolism is either so mild or so rapidly fatal that such signs are not present or the patients are examined only after the height of the effect of the pulmonary arterial obstruction has passed.

4. Pulmonary embolism and infarction are easily overlooked, especially in the presence of congestive heart failure, when they are most common; or they are erroneously diagnosed as something else, especially pneumonia, congestive heart failure, or coronary thrombosis.

5. Clues to the diagnosis lie in the occurrence of unexplained fever, leukocytosis, tachycardia, faintness, prostration, dyspnea, or even jaundice (from hemolysis of the infarct plus an engorged liver) especially in a cardiac patient with heart disease (and particularly in the presence of mitral stenosis or heart failure).

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COBRA VENOM.

Its Use in Stenocardia.

Preliminary Report.*

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The tremendous strides made in the diagnosis of coronary disease both clinically and graphically have become part of the accumulated

* We are indebted to Hynson Westcott & Dunning, Inc., of Baltimore, for their generosity in furnishing all the material for this study.

history of medical progress. However, the treatment of the condition has not kept step and has lagged far behind, as we all sadly realize. For the acute attack of coronary thrombosis our entire armamentarium may almost be summarized by one word—morphine. Be this as it may, the clear-thinking physician soon realizes that, though the double-edged sword of the opiates may be used in the original attack, the danger of habituation is too great to allow him to use the drug at frequent intervals for stenocardia of the lesser degree from which patients frequently suffer. This type of stenocardia is seen very often during the first 2 weeks following the onset of the thrombosis even while the patient is resting quietly in bed, and is also seen lasting for short periods at times, even months or years after the initial attack. Though many drugs have been suggested and used for the relief of this most trying pain, none has been very successful until the advent of cobra venom which, if it fulfills its original promise, will place us one step higher in our climb to successful treatment of those unfortunates who have stenocardia while at rest.

Though some venoms have been used in medicine for various purposes, there is one group, that of the cobra, which exerts an influence in a very important direction, namely, on pain. It is gratifying to note that it was an American physician, Adolph Monaelesser, who became interested most particularly in these venoms. At the Pasteur Institute he, Calmette, Oliverra, and Dumatras prepared the groundwork for the use of cobra venom in the relief of intractable pain of various causes.[6a] Dr. David Macht, who has had much experience with cobra venom and has been instrumental in developing its pharmacology in the treatment of painful conditions,[6b,c] suggested its use in the relief of those suffering from repeated attacks of stenocardia while at rest. He had made careful studies of the physiologic, pharmacologic, and psychologic effects of this venom and found that the drug could be prepared in a stable form and biologically assayed.[6d] Furthermore, the drug acted upon the higher nerve centers to produce its analgesia, being in this respect similar to morphine, differing from it, however, in that it was not habit-forming nor did it produce the mental depression of the opiate. In fact, mental efficiency seemed to be somewhat stimulated by cobra venom.[6e,8a] As part of this same mental stimulating factor, it is worthy of note that, whereas morphine and the other opiates contract or narrow the fields of vision, cobra venom widens them.[8b] The drug also differs from morphine in several other ways. In the first place, morphine acts very quickly after its administration; cobra venom, on the other hand, may take many hours or even a day before its action will be manifest. Further, morphine loses its effect within a few hours, whereas cobra venom has a rather marked cumulative effect which can be put to excellent advantage in treatment.[6d] In one respect, aside from its analgesic

action, cobra venom is similar to morphine; they both depress the respiratory center. Though in the therapeutic doses used there is very little danger of harmful depression of this vital center, nevertheless it is a point that must be kept in mind whenever the drug is employed.[6c] In order to reassure the physician as to the leeway between the usual therapeutic dose and one which may depress the vital respiratory center, several personal communications from Dr. Macht are illuminating. Five mouse units is considered to be the usual human starting dose; however, a number of physicians have administered 10 mouse units of the venom daily for from 1 to 3 weeks without in any way depressing the respiratory center. A few have even given 15 mouse units daily for several days. One physician reports the administration of 25 mouse units of cobra venom daily to a patient having most severe pain from generalized bone metastases from a breast cancer and states that he observed no ill-effect. In other words, cobra venom has been given in doses from two to five times that which is considered a safe starting dose with absolutely no evident depression of the vital respiratory center. The therapeutic dosage of the cobra venom is comparatively so small and the margin of safety so wide that there is little danger of medullary paralysis. So far, in fact, in spite of increasing use and dosage of the venom, no reports of respiratory embarrassment have been received. The only other reactions worth mentioning are purely local ones at the site of injection and are probably due to the tri-cresol added to the solution.[6c] Before leaving this phase of the discussion, it is pertinent to add that in experimental work conducted on rabbits, tremendous doses of venom failed to demonstrate any untoward effects upon kidney or liver function.[7] Though cobra venom is rather poor in cytotoxic elements compared to other venoms, it is exceedingly important to rule out any danger from this source. Huge doses of cobra venom injected into rabbits both intramuscularly and intravenously produced no significant changes in the blood cytologic or chemical picture.[9] In addition to these painstaking studies of Macht, articles by other investigators have appeared both here and abroad, all referring to the use of the venom for a variety of painful conditions and stressing the apparent lack of harmful side effects.[2–5,10–14]

Supported by this weight of evidence and by the fact that Bullrich,[1] in South America, had used the drug in certain types of angina pectoris, we felt justified in attempting to give our treatment-resistant patients this non-habit forming drug, apparently capable of relieving their repeated attacks of stenocardia.

At this time we have used the drug in but a small group of 5 cases with stenocardia at rest. These patients are not too common but present a problem which taxes and baffles the physician who finds himself between the Scylla of morphine addiction and the Charybdis of exhausting pain. We wish to report this group because cobra

venom was the only drug which gave them freedom from pain after all the other therapeutic agents except morphine failed. The nitrites, xanthine derivatives, papaverine, and other supposed coronary dilators were used in almost every case with very little or indifferent effects. Therefore, we feel that if we could get beneficial results in this group, the promise of the drug is too great to withhold until more numerous and detailed clinical studies can be performed.

Our patients were given 5 mouse units intramuscularly as the initial dose. This was repeated on the following 2 or 3 days. Then 1 ampule was given every other day for 5 or 6 doses. Finally, the dosage was reduced to 5 mouse units once or twice weekly. It is pertinent to note that Steinbrocker[13] has given as much as 10 and 15 mouse units in many of his cases without ill-effects. In other words, as with any drug, the dose must be increased until the desired therapeutic effect is achieved without producing toxic symptoms.

The cases selected by us represent stenocardia in its varied aspects.

Case Abstracts. Case 1.—A white woman, aged 69, complained of attacks of precordial pain radiating to the left shoulder and accompanied by a sense of constriction in the throat. The cardiac examination was negative except for a blood pressure of 180 systolic, 90 diastolic, a pulse rate of 108 per minute, and an electrocardiogram which showed evidences of myodegeneration. On August 6, 1939, she was given 2.5 mouse units of cobra venom, followed by 5 mouse units on the 2 following days and then 5 units every other day for 3 weeks. After 2 days of treatment, her attacks were reduced to 1 a day from a level of 10 to 12. At the end of 2 weeks all attacks disappeared, and the cobra venom was stopped 1 week later. On her last visit her blood pressure was essentially the same and her electrocardiogram showed no regressive changes.

Case 2.—A white laborer, aged 54, had had attacks of substernal pressure for some months before he was first seen on October 22, 1938. By that date these attacks were coming on even at rest, each lasting 10 to 30 minutes. This patient had a blood pressure of 225 systolic, 125 diastolic, tortuous fundal vessels, cardiac enlargement to the left and a soft blowing systolic mitral murmur. The electrocardiogram showed the usual changes seen in hypertension. During the next year he had at least one or two attacks of substernal pressure daily while at rest as well as whenever he walked. On October 12, 1939, he received 5 mouse units of cobra venom and this dose was repeated on 5 successive days. At this point he was free of pain for the first time in over a year. The dose was then reduced to 1 ampule every other day for 2 weeks and then to 2 ampules weekly. At the end of 4 weeks, the dose was reduced to 1 ampule weekly. This was enough to keep him free of pain while at rest, but he still had an occasional seizure while walking. When last seen in March, 1940, the patient showed no electrocardiographic or physical damage as a result of the cobra venom.

Case 3.—A white woman, aged 60, had had a coronary occlusion 3 months before her first visit on February 10, 1940. She was then suffering from attacks of severe substernal pressure radiating into the left arm, severe enough to awaken her from sleep. She had a blood pressure of 220 systolic, 110 diastolic, a systolic blow over the mitral area and an electrocardiogram which showed a left bundle-branch block. There was no cardiac enlargement. Since she was seen in consultation, she was treated by her family physician who gave her 5 mouse units on 3 successive days and then 1 am-

pule every other day for 2 weeks followed by 2 ampules weekly thereafter. A letter from him states that she had had marked relief since the use of the cobra venom though she still gets an occasional attack. Here too, there has been no cardiac damage, as shown by the electrocardiogram, from the use of cobra venom.

CASE 4.—A white male, aged 51, was first seen in consultation in 1934. He was then complaining of pain in the precordium which usually came on during effort, but was occasionally also present at rest. Physical examination was negative at that time except for some cardiac enlargement to the left and a blood pressure of 115 systolic, 70 diastolic. A diagnosis of angina pectoris was made. In these 6 years the patient has had many periods during which his pain was so severe for several days at a time that only morphine gave him relief. He started another such bout on October 20, 1939. Five mouse units of cobra venom were given him daily for 3 days before he experienced any relief. An ampule was given him twice daily thereafter until November 30, when treatment was stopped. The patient was free from pain during this entire period for the first time since 1934. He returned again on January 3, 1940, complaining of having had pain during the last 2 weeks of December. He was given two injections of cobra venom with such singular relief that he did not return until March 9. Once more he received the venom, every other day for three doses and then twice weekly for about 1 month, again with complete relief of pain.

CASE 5. A white male, aged 61, had had coronary occlusions in 1934 and in 1938. On January 24, 1940, he developed acute cardiac failure, which was controlled readily with morphine and aminophyllin intravenously. On January 26, however, he suffered another coronary occlusion. After this, he began to have one or two attacks of such severe substernal pressure nightly that morphine was necessary for relief. Finally, after all other remedies but morphine were found inadequate, cobra venom was started on February 22, 1940. He received 1 ampule daily for three doses and then every other day for 3 weeks. Thereafter, he received 1 ampule weekly with adequate control of his pain. It was only after the cobra venom began to give him relief from pain, that the patient showed clinical improvement. Blood counts and electrocardiograms failed to show any damage from the cobra venom.

We wish to emphasize that, though 5 cases are very few, they were all patients who were either very ill or upon whom every other type of medication had been used to little or no avail. Therefore, if cobra venom could work here, it could be expected to work successfully in a large percentage of similar cases. This work is being carried further as cases become available.

Let us reëmphasize the fact that cobra venom cannot be used to relieve the pain of an acute attack of coronary thrombosis, since its action is slow and cannot be expected to reach its full effect a few hours after an injection. In fact, it may sometime take 24 to 48 hours for the drug to become effective at all. The user must never expect his patient to be relieved of symptoms until at least 2 or 3 injections have been given. It can be readily seen, therefore, that by no stretch of the imagination can this be considered an emergency measure.

Though Macht[65] has reported some unfavorable reactions from the drug, as has Steinbrocker,[13] in our group we have noted none. The only complaints were those that follow any intramuscular

injection. Several of the patients, when they discovered the nature of the drug they were receiving, had slight psychologic misgivings which were soon corrected by reassurance.

Summary. We have used a new drug, cobra venom, in certain cases of stenocardia which were helped by no other medication but morphine. All 5 cases were relieved of their symptoms when adequate doses of the drug had been given. No untoward reactions were observed. We are convinced that a valuable therapeutic agent has been added to the armamentarium of the cardiologist for the relief of stenocardia.

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HEREDITY IN PERNICIOUS ANEMIA.

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The importance of heredity as a factor in the pathogenesis of disease has long been recognized. Evidence is accumulating that the hereditary occurrence of pernicious anemia is more than merely a coincidental curiosity.

In 1891, Klein[12] reported the presence of Addisonian anemia in 4 members of one family, a sister and 3 brothers. In 1899, Bramwell[2] mentioned the occurrence of the disease in a patient and his brother, mother, 2 uncles and an aunt. Caccini,[4] in 1900, reported the presence of this disease in a father, son and daughter. In 1908, after a review of 1200 cases, Cabot[3] concluded that the "disease did not appear to be hereditary." In 1907, Gulland[8] called attention to 3 patients whose father had died of pernicious anemia. In 1911, Patek[13] referred to the presence of pernicious anemia in 2 brothers, a sister, paternal aunt and cousin. In 1913 Bartlett[1] reported its occurrence in a father and 3 sons. Gulland and Goodall,[9] with a personal experience of approximately 500 cases, reported that pernicious anemia not uncommonly occurs in more than one member of the same family.

It is noteworthy that this apparently hereditary incidence in pernicious anemia was merely mentioned as an incidental and curious phenomenon.

In 1920 Minot[16] did not consider the occurrence of pernicious anemia in members of the same family as common, and regarded the hereditary factor as unimportant.

As early as 1918 Schauman[19] regarded the hereditary incidence of pernicious anemia as a frequent and important factor. In 1921 Levine and Ladd[13] discovered a distinct familial incidence in pernicious anemia while studying 143 cases. Nine patients were stated as having a "definite family history" of the disease in some other member of the family. In 1927 Minot[15] stated that while pernicious anemia "may occur in the same family, this is unusual." But in 1936 Castle and Minot[5] noted that "when complete histories are available, at least 18 per cent of the patients will be found to have one or more close relatives who have the disease." Meulengracht[14] believes that heredity plays an important rôle in the disease, but feels that more work is necessary before this point can be proved.

There is an increasing tendency in more recent literature to regard the hereditary incidence in pernicious anemia as an important factor in the pathogenesis of the disease. Publications by Gilford,[7] Meulengracht,[14] Hurst,[10] Dorst[6] and Schemm[20] tend to support this view. Mustelin[17] has advanced the hypothesis that pernicious anemia is a dominant property, depending on a single gene. Kaufmann and Thiessen,[11] in a study of the subject, conclude that the disease is transmitted as a dominant characteristic; they believe there are members of families who do not have pernicious anemia but are "carriers" of the disease from the hereditary standpoint.

In any study of the hereditary incidence in pernicious anemia there are a number of inherent difficulties which confront the observer. Among these may be mentioned: 1, errors in diagnosis; 2, difficulty in pursuing thorough investigation due to scattering of families; 3, failure to recognize pernicious anemia as a cause of death in some families; 4, deaths from accidents or disease early in the life of members of a family may affect the statistics; 5, being a disease that occurs in the later decades of life, members of a family not having the disease may eventually show evidence of it.

In an analysis of 645 unselected, authenticated cases of pernicious anemia at this Institute, 51 case histories revealed the presence of the disease in one or more other members of the same family. This gives an incidence of 7.9%. In 8 of these 51 family histories, the diagnosis of pernicious anemia in other members of the family was also made at this Institute; in 8 the diagnosis was made by the family physician. In the remaining 35 cases, the patient's report of the disease in his family was the sole method available for establishing a positive family history. It is obvious, therefore, that the true incidence in this series of 645 cases is probably less than 7.9%, inasmuch as some of the cases diagnosed as pernicious anemia and

reported only through the patient may have had some other type of anemia.

TABLE 1.—THE OCCURRENCE OF PERNICIOUS ANEMIA IN 51 FAMILY HISTORIES.

Other members of family having pernicious anemia.	No. of families.	Total No. of individuals having pernicious anemia in 51 families.	Members of family known to have died of pernicious anemia.
Mother	10	20	8 of 10 mothers
Father	8	16	6 of 8 fathers
Sister	11	22	3 of 11 sisters
Brother	5	10	3 of 5 brothers
Case of twins; no other family member has pernicious anemia	1	2	None
Two brothers	2	6	2 brothers 1 brother
Brother, sister	3	9	None Brother and sister None
Uncle	1	2	None
Father, brother	1	3	Father, brother
Paternal aunt	1	2	None
Paternal grandfather Brother	1	3	Paternal grandfather Brother
First cousin	1	2	None
Mother, uncle, maternal aunt, sister	1	5	Mother, uncle, maternal aunt
Father, paternal uncle, one of twin sisters	1	4	Father
Mother, 2 maternal aunts	1	4	Mother, 2 maternal aunts
Two brothers, 1 sister	1	4	Two brothers
Mother, sister	1	3	Mother, sister
Mother, uncle, maternal aunt, sister	1	5	Mother, uncle, maternal aunt
Father, paternal uncle, one of twin sisters	1	4	Father
Mother, 2 maternal aunts	1	4	Mother, 2 maternal aunts
Two brothers, 1 sister	1	4	Two brothers
Mother, sister	1	3	Mother, sister
Mother, maternal grandmother, maternal aunt	1	4	Mother, maternal grandmother, maternal aunt

Of these 51 families the only other member, besides the patient, found to be affected was the mother in 10 instances, the father in 8, the sister in 11, and the brother in 5. Two family histories revealed the presence of pernicious anemia in an uncle and paternal aunt respectively.

Five families are represented in this series in which 3 or more of the immediate children had the disease. In one family the mother, uncle, and maternal aunt died of pernicious anemia, and the patient and her sister were diagnosed here as having the disease. In another family the paternal uncle died of pernicious anemia, the father, and one of twin sisters, and the patient were diagnosed here as having this disease. A mother and 2 maternal aunts of a patient died of pernicious anemia in another family. One case history revealed the death of a mother, maternal grandmother and maternal aunt.

Two families were particularly interesting. In one of these, twin sisters, age 35, the only siblings, were here diagnosed as having pernicious anemia. In the other, a family of 4 children, 2 brothers died of the disease and 2 sisters were here diagnosed as having pernicious anemia. The father of this family died "cause unknown" and the mother died of "dropsy." One of these sisters had 8 children who were said to be in good health, ages not given.

In a study of 377 patients with pernicious anemia at this Institute, Dr. Lloyd R. Gates asked the patients "Did any of your relatives have pernicious anemia?" Of these, 27.3% answered "Yes," and 72.1% answered "No." In 536 patients of a similar age and location group, but who did not have pernicious anemia, the answers to the same question were "Yes" 9.1% and "No" 90.9%. These data, of course, do not indicate that the relatives actually had Addisonian pernicious anemia, but they are suggestive, inasmuch as the same type of error (false diagnosis) could be present in the control series as well as the pernicious anemia group. In both of these groups, however, the observed difference was 2.5 times its standard error.

The hereditary incidence in this series of cases is 7.9%. It does not approach the 18% figure given by Minot and Castle. Although the former percentage is minimal, this study only includes a limited range of relatives. As Meulengracht has pointed out, pernicious anemia is relatively uncommon, and in his investigation of the family histories of a number of control individuals he gives the incidence as zero. The percentage of 7.9% is, therefore, too high to be due to mere chance. It is believed, however, that a similar series of cases more closely controlled would likely reveal a higher incidence. Furthermore, the repeated occurrence of the disease in several members of the same family does not appear to be due to chance alone.

Another view of the problem, using these data, is that 92.1% of

the patients with pernicious anemia knew of no hereditary involvement. In other words, a patient may be advised that there is over 92% chance that his children will not have pernicious anemia; and that there is the same chance that if his parents had pernicious anemia, he would not have it. The question as to whether multiple cases in one family are fortuitous or the result of a hereditary tendency to the disease, or to a common abnormality in the environment, is still not clear. The peculiar anthropomorphic characteristics which patients with pernicious anemia have would make it seem that at least some of the "soil" of the disease is familial.

Summary. In a series of 645 cases of pernicious anemia the percentage of familial incidence is 7.9%. In this series 5 families are represented in which 3 or more of the immediate children had the disease. Five additional families reveal the presence of pernicious anemia in 3 or more members of the same family in successive generations among the lineal or collateral descendants. An authenticated instance of the disease occurring in twin sisters is reported.

It is suggested by this study that a definite familial hereditary factor exists in pernicious anemia. Continued interest and investigation of this question are advisable because of its obvious practical significance.

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THE EFFECT OF NICOTINIC ACID ON BLOOD COAGULATION.

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In a previous paper,[1] it was reported that the blood of patients suffering from chronic brucellosis often clots slowly, retraction of the coagulum is imperfect, and the yield of serum is low. Adminis-

tration of nicotinic acid to such patients was followed by complete correction of these defects.

The addition of nicotinic acid *in vitro* to samples of whole blood from 6 brucellosis patients showing this abnormality (0.6 mg. per cc. blood) reduced the clotting time from an average of 11.3 to 6 minutes and clot retraction, imperfect or absent in the controls, was complete within 3 hours in all instances. Likewise, the clotting time of plasma from 25 brucellosis subjects was reduced an average of 36% by the addition of similar concentrations of nicotinic acid *in vitro*.

When a solution of nicotinic acid (0.6%) was applied by cotton pledget to tooth sockets following extraction, a firm, permanent clot resulted in from 1 to 2 minutes; untreated control sockets on the same patient followed the usual course, often bleeding for several hours. Similarly, local application to small cuts caused an immediate stay of blood flow.

The internal use of nicotinic acid in 2 cases of typhoid fever was followed by striking disappearance of delirium, coma, and intestinal bleeding. In 1 of these cases, due to a mistake in orders, nicotinic acid was discontinued after 10 days, during which time the patient seemed to be convalescing perfectly; within 24 hours delirium recurred, and intestinal hemorrhage with death ensued.

In another patient, who had suffered for years from profuse and prolonged nosebleeds, it was found that, except for a barely detectable coagulum at 20 minutes, the blood was still fluid at 24 hours. Oral administration of 100 mg. nicotinic acid 3 times daily was followed by a clotting time of 6 minutes; and in the 4 months during which this treatment was continued, there was no recurrence of bleeding.

One patient, diagnosed as having hypoplastic anemia, had a bleeding time of 15 minutes without prolongation of clotting time (2 minutes). After oral administration of nicotinic acid for 1 week (100 mg. 3 times daily) the bleeding time was 8 minutes.

A 13-year-old male patient, ill for 9 months with low-grade fever of unknown etiology, exhibited marked tendency to bleed. The platelet count had varied from 25,000 to 50,000 during this illness. He bled so profusely from a small puncture wound made in the ear for test purposes that more than 100 sheets of filter paper were soaked with blood in the 35 minutes before bleeding was stopped mechanically. After oral administration of 100 mg. nicotinic acid 3 times daily for 1 week, the bleeding time was reduced to 15 minutes and only 3 sheets of filter paper were required to absorb the blood lost in the test.

The addition of nicotinic acid to blood samples from 3 patients with acute catarrhal jaundice (0.12 to 0.6 mg. per cc. of blood) reduced the clotting time from an average of 14 to 6 minutes. On

blood from a patient with hemophilia nicotinic acid had no effect when added *in vitro*.

Experimental Observations. In an effort to elucidate the mechanism responsible for the above results, experiments were performed to determine whether nicotinic acid can be substituted for any of the factors involved in normal coagulation. According to Eagle,[2a] calcium and platelets (or other tissue extracts) appear to constitute a proteolytic enzyme which converts prothrombin to thrombin, and the latter then causes the transformation of fibrinogen to fibrin. By preparing these various reagents in purified form, it was possible to compare their action, separately and in different combinations, with that of nicotinic acid. The following experiments indicate that the action of nicotinic acid does not duplicate that of any of these factors.

Thromboplastin was prepared by Quick's[4b] method; prothrombin by Mellanby's technique (Eagle[2b]) or Eagle's method (Tillett[5]); and purified fibrinogen by Eagle's[2c] procedure.

In this series of experiments, it was found that oxalated plasma could not be made to clot by the addition of any concentration of nicotinic acid (0.1% to 0.6% in the final mixture); hence nicotinic acid is not equivalent to calcium. Likewise, plasma from which the platelets were removed by filtration could not be clotted with similar concentrations of nicotinic acid; it is evident, therefore, that the action of nicotinic acid does not duplicate that of platelets.

Nicotinic acid is also not the equivalent of the thromboplastic principle found in tissue extracts. The addition of thromboplastin to 6 samples of plasma caused clotting in 19 seconds; while, when nicotinic acid (1.2 mg. to 1 cc. plasma) or physiologic saline was used, the clotting time averaged 139 seconds.

Nicotinic acid does not convert prothrombin to thrombin. Buffered (pH 6.8) prothrombin, subjected for 15 minutes to the action of nicotinic acid and then added to purified fibrinogen, failed to induce clotting, even after the addition of calcium.

Nicotinic acid does not increase the yield of thrombin from prothrombin: 0.6 mg. of nicotinic acid and 0.1 cc. of 2.5% calcium chloride were added to 1 cc. of prothrombin solution.[5] The resulting solution was diluted and added to 0.2 cc. plasma in amounts varying from 0.1 to 0.005 cc., at which point the material was inactive. At each dilution, the behavior of the thrombin obtained from the specimen containing nicotinic acid was identical with that obtained from the saline extractive.

Finally, nicotinic acid does not duplicate the action of thrombin itself, for purified fibrinogen buffered at pH 6.8 was not clotted by the addition of nicotinic acid (0.1% to 0.6% in the final mixture).

Apparent Neutralization of Antithrombin by Nicotinic Acid. Since it is known that antithrombin inhibits blood clotting, experiments were devised to determine whether nicotinic acid would induce

the coagulation of blood in which the antithrombin content was increased. This abnormality was produced by adding heparin (Hynson, Westcott and Dunning; 0.2 mg. per cc. of blood) to human blood, and also by shocking dogs by anaphylaxis[3] or peptone.[4a] Under these conditions, it is well established that the failure of the blood to clot is due to its increased content of antithrombin; and if nicotinic acid could induce coagulation of such blood, it would be reasonable to assume that neutralization of antithrombin had occurred.

Non-coagulable blood from 2 dogs in anaphylactic shock clotted in 4 minutes after the addition of 2.5 mg. nicotinic acid per cc. of blood.

Nicotinic acid failed to shorten the coagulation time significantly in 9 of 31 samples of blood from dogs in peptone shock. In the remaining 22 instances, however, samples containing nicotinic acid clotted in an average of 17 minutes, whereas none of the controls clotted in less than 12 hours and many remained fluid after 24 hours (Table 1). The concentrations of nicotinic acid required to produce this effect varied in different samples, probably due to the varying amounts of antithrombin present; in most instances, 3.3 mg. of nicotinic acid per cc. of blood was used.

TABLE 1.—EFFECT OF NICOTINIC ACID *in Vitro* ON BLOOD OF DOGS IN PEPTONE SHOCK.

Clotting time in minutes.		Concentration N. A. in mg. per cc. of blood.
Without N. A.	With N. A.	
∞	C 1.5	0.5
P 200	C 12	6.0
∞	C 6	6.0
P 720	C 6	3.3
∞	C 8	3.3
P 720	C 10	3.3
P 265	C 6.5	3.3
P 720	C 17	3.3
P 720	C 20	3.3
P 316	C 8	3.3
Sl 720	C 60	3.3
P 720	C 7	3.3
C 720	C 8	2.5
C 720	C 7	2.5
P 720	C 11	3.3
∞	C 35	1.5
Sl 720	C 5	1.5
∞	C 67	2.0
∞	C 9	1.5
∞	C 13	2.0
∞	C 13	1.5
∞	C 36	2.0

Abbreviations (in all tables): N. A. = Nicotinic acid; Sl = slight trace of coagulum; P = partial clot, not holding on inverting tube; C = complete, firm clot.

In 5 samples of heparinized human blood the coagulation time was reduced by nicotinic acid (6 mg. per cc. of blood) from partial clotting at 40 minutes (average) to complete clotting at 10 minutes (average) (Table 2).

TABLE 2.—COMPARISON OF COAGULANT ACTION OF NICOTINIC ACID WITH THAT OF OTHER ACIDS. HEPARINIZED BLOOD.

Acid.	Heparin (mg.).	Saline (cc.).	Results.				
			Subject A.	Subject B.	Subject C.	Subject D.	Subject E.
0 (normal control) . .	0	1.0	P 4 C 7	P 5 C 7	C 8	P 9 C 12	P 5 C 8
0 (heparin control) . .	0.2	0.9	Sl 33 P 37	P 38	P 60	P 32	P 33
Nicotinic 9 mg. (0.9 cc. 1%)	0.2	0	C 11	C 8	P 8 C 10	P 9 C 12	P 8 C 10
Acetic	0.2	0	P 18	P 22	P 23	P 35	P 25
Citric	0.2	0	P 22	P 25	P 30	Sl 27 P 31	P 25
Lactic	0.2	0	P 17 C 26	P 15	P 35	Sl 27 P 39	P 21
Oxalic	0.2	0	P 26	P 18	P 31	P 27	P 21
Hydrochloric . . .	0.2	0	P 32	P 34 C 38	P 60	Sl 36 P 50	P 37 C 46
Nitric	0.2	0	P 23	P 31	P 31 C 40	P 23	P 21
Sulphuric	0.2	0	P 23	P 23	P 24	P 28	P 17 C 21

1.5 cc. whole blood in each tube. Volume and pH of other acids duplicated those of nicotinic acid.

TABLE 3.—COMPARISON OF COAGULANT EFFECT OF NICOTINIC ACID WITH THAT OF OTHER ACIDS (BLOOD FROM DOGS IN PEPTONE SHOCK; *in Vitro*).

Dog No.	Clotting time (saline control).		Clotting time after addition of various acids.							
	Before shock.	After shock.	Nicotinic.	Acetic.	Citric.	Lactic.	Oxalic.	Hydrochloric.	Nitric.	Sulphuric.
1	8	P 265	C 6.5	P 12	P 103	P 170	P 720	P 265	P 11	P 265
2	6	P 720	C 17	P 65	P 720	Sl 720	Sl 720	Sl 720	P 380	Sl 720
3	8	∞	∞	P 360	∞	∞	∞	∞	Sl 720	∞
4	6	Sl 720	C 720	P 720	P 720	∞	Sl 720	∞	Sl 405	Sl 720
5	3.5	P 720	C 720	Sl 720	Sl 720	P 720	P 720	Sl 720	P 720	Sl 720
6	3	P 720	C 20	C 20	C 720	C 720	C 720	P 305	C 720	C 720
7	3	P 316	C 8	C 8	Sl 109	∞	∞	∞	P 26	Sl 271
8	2.5	Sl 720	C 60	C 60	C 720	C 720	Sl 720	P 720	P 271	P 720
9	4	∞	P 720	P 720	Sl 720	Sl 720	Sl 720	Sl 720	P 720	Sl 720
10	2	Sl 720	C 720	P 60	Sl 720	∞	∞	∞	Sl 720	Sl 720
11	2	P 720	P 720	P 42	P 720	Sl 720	Sl 720	Sl 720	P 720	Sl 720
12	5	P 720	C 7	P 6	P 720	P 720	P 720	P 720	P 720	P 720
13	2	C 720	C 8	C 720	C 720	C 720	C 720	C 720	C 720	C 720
14	2	C 720	C 7	C 7	C 720	C 720	C 720	C 720	C 720	C 720
15	2.5	P 720	C 11	P 11	P 720	P 720	P 720	P 720	P 720	P 720
16	1	Sl 720	C 5	C 5	∞	∞	∞	∞	P 5	∞
17	1	∞	C 67	Sl 720	∞	∞	∞	∞	∞	∞
18	4	∞	C 9	Sl 720	∞	∞	∞	∞	∞	∞
19	1.5	∞	C 13	Sl 720	∞	∞	∞	∞	∞	∞
20	1	∞	C 13	C 13	∞	∞	∞	∞	Sl 720	∞
21	1	∞	C 38	∞	∞	∞	∞	∞	∞	∞
22	2.5	∞	C 720	∞	∞	∞	∞	∞	∞	∞

Nicotinic acid was added in the form of saturated solution (1%), in saline, the final concentration being 1.5 mg. per cc. of blood. Other acids were made up in normal saline and pH adjusted colorimetrically to duplicate that of the nicotinic acid solution.

In order to check on whether the observed effects were due simply to non-specific alteration of hydrogen-ion concentration, other acids were used (acetic, citric, lactic, oxalic, hydrochloric, nitric and sulphuric). These were made up in such concentrations as to duplicate the pH of the corresponding nicotinic acid solutions as determined colorimetrically. Comparison of the effect of these acids was made in a series of heparinized human blood samples (Table 2) and a series of samples from dogs in peptone shock (Table 3). Since the other acids used are all stronger than nicotinic acid, the final acidity of the blood mixtures would be greater than that attained with nicotinic acid. Nevertheless, only in an occasional instance in which acetic or nitric acids were used, was coagulation accelerated. This effect of these acids is probably to be attributed to their destructive action on the red cells, the stroma of which might well serve as mechanical foci from which clotting proceeds (Table 2).

Discussion and Summary. Clinical experience in a significantly large group of patients with chronic brucellosis revealed that nicotinic acid possesses the property of promoting coagulation of the blood. These patients often develop subcutaneous hemorrhages after slight trauma, and their blood clots slowly, retraction is imperfect, and the yield of serum is low. All of these defects were completely remedied by the administration of nicotinic acid.

These observations were extended to a small group of patients with other clinical states associated with bleeding, and the results were uniformly encouraging. Presumably, the hemorrhagic tendencies in all of these patients rested on a toxic, infectious basis. We have not as yet had opportunity to try this material in the various blood dyscrasias in which its possible effect would be of obvious interest and importance.

Experimental studies reported herein show that nicotinic acid does not duplicate the action of, nor can it be substituted for, any of the known factors involved in blood clotting (calcium, platelets, thromboplastic principle, prothrombin, or thrombin). However, when it is added *in vitro* to blood containing excessive amounts of antithrombin (heparinized blood or samples from dogs in peptone or anaphylactic shock), it does induce coagulation. That this effect is not due to non-specific alteration of hydrogen-ion concentration was indicated by contrast of nicotinic acid with seven other acids, none of which was as active in this respect as was nicotinic acid.

The quantities of nicotinic acid employed in our *in vitro* experiments were so enormous when compared with the doses used clinically, that it is not justifiable to assume that the mechanism of its effect in patients is necessarily a chemical neutralization of antithrombin, though such an explanation is possible. Certainly, in view of the small doses effective in patients, the results cannot be attributed to a non-specific acid effect. It would seem logical, we

believe, to conclude that nicotinic acid corrects a fundamental deficiency in the organism; or, by some pharmacodynamic action (*e. g.*, stimulation of the liver), induces the formation either of more prothrombin or of less antithrombin.

Whatever the mechanism of its action may be, our experiences indicate that further trial of nicotinic acid in various hemorrhagic states is warranted.

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CULTURE OF HUMAN MARROW.

STUDIES OF THE RELATIVE EFFECTIVENESS OF NEOARSPHENAMINE, MAPHARSEN, SULFANILAMIDE, SULFAPYRIDINE, SULFATHIAZOLE, AND SULFAMETHYLTHIAZOLE ON INFECTIONS WITH STREPTOCOCCUS VIRIDANS (ALPHA HEMOLYTIC STREPTOCOCCUS).*†

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THE marrow culture method[7] is well adapted to controlled quantitative studies of the relative effectiveness of therapeutic agents on infections in the presence of living human cells.[1,6a–c,e] It seemed important to study the *Strep. viridans* because it is the major cause of subacute bacterial endocarditis, a disease with an almost 100% mortality, and because no reports were found in the literature which indicated that under controlled conditions any therapeutic agent in a concentration which would not kill human cells would

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lead to the death of these organisms. Neoarsphenamine, mapharsen, sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole were chosen for study because of their known effectiveness against other organisms and because neoarsphenamine, sulfathiazole and sulfamethylthiazole have been found to be more effective in staphylococcus infections than sulfanilamide or sulfapyridine.[6d-f]

Method. Cultures of human bone marrow were prepared as previously described.[7] To about 50 cc. of culture containing about 100,000,000 nucleated marrow cells in one vial was added with syringe and needle a dilution of a culture in Hartley broth of *Strep. viridans*. After thorough mixing pour plates were made for colony counts, and equal volumes (about 8 cc.) were then transferred to each of a number of 30-cc. vaccine vials. This insured that each vial contained the same number of the same strain of organisms and the same number of cells in identical medium. To each of these, except the control, enough of the drug to be studied was added to give the desired concentration. The cultures were then placed in the incubator at 37° C., and pour plate counts and smears were made at intervals. This technique insures that the only variable is the presence of the drug.

TABLE 1.—COMPARATIVE EFFECTIVENESS OF DIFFERENT CONCENTRATIONS OF NEOARSPHENAMINE (STRAIN 3 IN TABLE 7).

	Colony counts.			
Hours:	0.	6.	24.	96.
Control	10	2500	300,000,000	
Neoarsphenamine,* 1:50,000	10	5?†	5?	0
Neoarsphenamine, 1:75,000	10	6?	0	0
Neoarsphenamine, 1:100,000	10	0	0	0
Neoarsphenamine, 1:200,000	10	15?	300	10
Neoarsphenamine, 1:400,000	10	100	100,000,000	

* In concentrations greater than 1:75,000 the marrow cells were destroyed.

† In this and all subsequent tables the question mark indicates colony counts based on less than 20 or more than 500 colonies on a pour plate.

TABLE 2.—COMPARATIVE EFFECTIVENESS OF SULFANILAMIDE, SULFAPYRIDINE AND NEOARSPHENAMINE* (STRAIN 4 IN TABLE 7).

	Colony counts.		
Hours:	0.	6.	24.
Sulfanilamide, 1:10,000	20	>2500	10,000,000
Sulfapyridine, 1:20,000	20	>2500	8,000,000
Neoarsphenamine, 1:200,000	20	15	0

* Note that neoarsphenamine was more effective than sulfanilamide and sulfapyridine.

Results. Examples of the results are shown in Tables 1 to 6 and in Figures 1 to 6. As has previously been shown[6d-f] concentrations of neoarsphenamine above 15 parts per 1,000,000 (or 1:70,000) killed all marrow cells, and concentrations of less than 2.5 parts per 1,000,000 (or 1:400,000) were ineffective in controlling infections. Concentrations of about 1:150,000 did not materially damage marrow cells and were very effective against most of the strains of *Strep. viridans*[6d,e] as shown in Tables 1 to 5. With the strains of organisms first tested, which gave results similar to those shown in Tables 2 and 3 and Figures 1 to 6, sulfanilamide, sulfapyridine and,

when tested, sulfathiazole and sulfamethylthiazole were relatively ineffective; whereas, neoarsphenamine and mapharsen were more effective. Preliminary reports based on these studies[6d,e] were made.

TABLE 3.—COMPARATIVE EFFECTIVENESS OF SULFAPYRIDINE, SULFATHIAZOLE, MAPHARSEN AND NEOARSPHENAMINE (STRAIN 5 IN TABLE 7).

	Colony counts.		
Hours:	0.	26.	46.
Control	2000	8,500,000	100,000,000
Sulfapyridine, 1:10,000	2000	4,000,000	100,000,000
Sulfathiazole, 1:10,000	2000	7,000,000	100,000,000
Mapharsen, 1:2,000,000	2000	1,500,000	100,000,000
Neoarsphenamine,* 1:10,000	2000	0	

* Due to an error in dilution a higher concentration of neoarsphenamine was used in this experiment than was intended. In several other experiments with this same strain neoarsphenamine in a concentration of 1:150,000 was effective. This experiment was selected, however, because a larger number of drugs were used or a greater number of colony counts were obtained than in the other experiments. See Figures 1 to 6 for the results of another experiment using this same strain. The patient from whom this culture was obtained has shown a good clinical response to therapy with neoarsphenamine and heparin, and she has had 5 negative blood cultures in the 6 weeks since therapy was discontinued.

TABLE 4.—COMPARATIVE EFFECTIVENESS OF SULFAPYRIDINE, SULFAMETHYLTHIAZOLE, SULFATHIAZOLE, NEOARSPHENAMINE, AND NEOARSPHENAMINE PLUS SULFATHIAZOLE* (STRAIN 6 IN TABLE 7).

	Colony counts.				
Hours:	0.	4.	24.	46.	48.
Control	20	44	1,120,000	>100,000,000	
Sulfapyridine, 1:10,000	20	2?	0	....	0
Sulfamethylthiazole, 1:10,000	20	0	0	....	0
Sulfathiazole, 1:10,000	20	0	0	....	0
Neoarsphenamine, 1:150,000	20	4?	2?	....	0
Neoarsphenamine, 1:150,000 plus sulfathiazole, 1:20,000	20	0	0	....	0

* All drugs were effective against this organism.

Subsequently, other strains were investigated (Tables 4 to 6) in which sulfapyridine, sulfathiazole and sulfamethylthiazole were also effective. One strain was found against which neoarsphenamine was

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LEGENDS FOR FIGS. 1 TO 6.

FIG. 1.—Control at 28 hours from a marrow culture experiment in which the same strain of *Strep. viridans* as that shown in Table 3 was used (Wright's stain, ×1200). Compare this with Figures 2 to 6 which are from the same experiment and were taken at the same time.

FIG. 2.—Culture containing 1:10,000 sulfapyridine (Wright's stain, ×1200). Compare with Figures 1 and 3 to 6.

FIG. 3.—Culture containing 1:10,000 sulfathiazole (Wright's stain, ×1200). Compare with Figures 1, 2 and 4 to 6.

FIG. 4.—Culture containing 1:10,000 sulfamethylthiazole (Wright's stain, ×1200). Compare with Figures 1 to 3, 5 and 6.

FIG. 5.—Culture containing 1:1,500,000 mapharsen (Wright's stain ×1200). Compare with Figures 1 to 4 and 6.

FIG. 6.—Culture containing 1:150,000 neoarsphenamine (Wright's stain, ×1200). Compare with Figures 1 to 5. This is the only culture which became sterile. Note that the cells were undamaged.

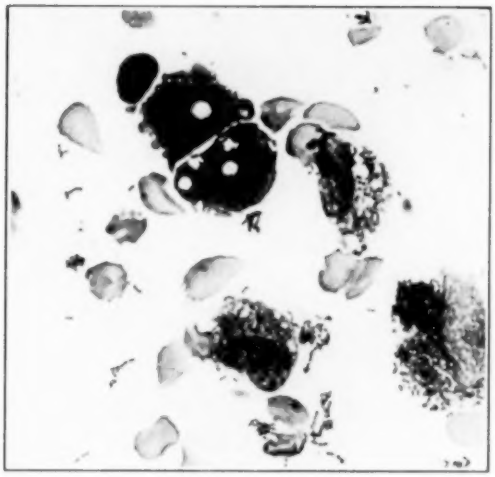

Fig. 1

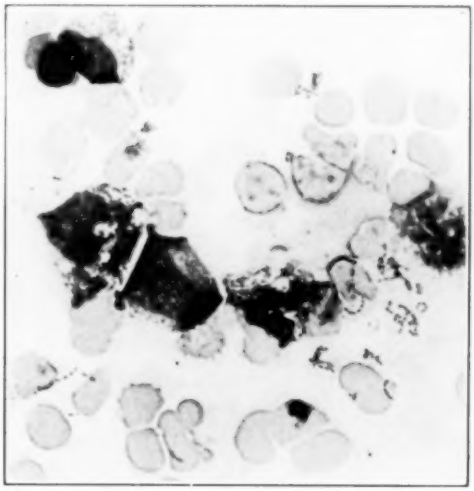

Fig. 2

Fig. 3

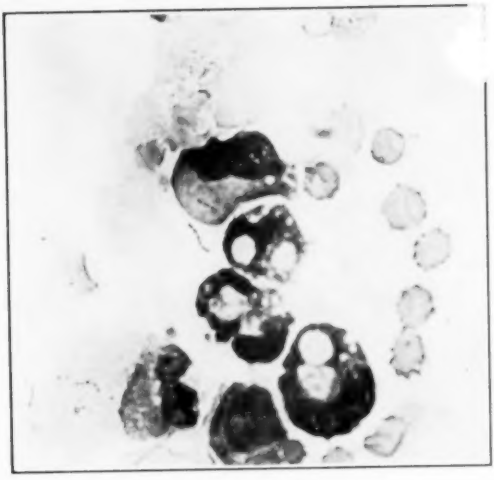

FIG. 4

FIG. 5

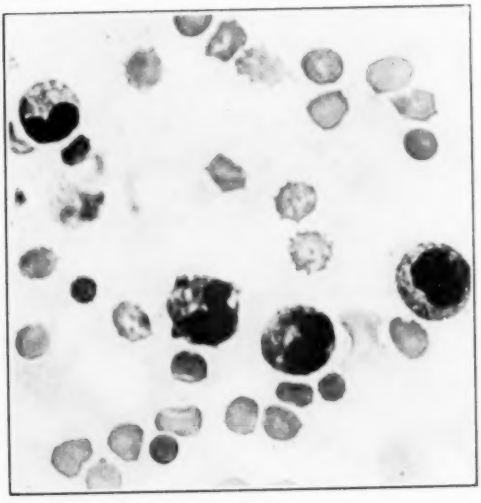

FIG. 6

entirely ineffective (Table 6). No cultural or morphologic characteristics were found which could distinguish the strains with different drug susceptibility from each other. Mapharsen in concentrations of 1:1,500,000 was as effective as neoarsphenamine in concentrations of 1:150,000 against some strains (Table 5) and not as effective against other strains (Table 3, Figs. 5 and 6). Sodium cacodylate and arsphenamine were not as effective as neoarsphenamine.

TABLE 5.—COMPARATIVE EFFECTIVENESS OF NEOARSPHENAMINE, MAPHARSEN, SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE (STRAIN 7 IN TABLE 7).

	Colony counts.				
Hours:	0.	4½.	27½.	48.	53.
Control	50	200	6,000,000	>100,000,000	
Neoarsphenamine, 1:150,000	50	50	400	....	200,000
Mapharsen, 1:1,500,000	50	100	500	....	100,000
Sulfathiazole, 1:10,000	50	20	0	0	0
Sulfamethylthiazole, 1:10,000	50	40	0	0	0

TABLE 6.—COMPARATIVE EFFECTIVENESS OF NEOARSPHENAMINE, SULFAPYRIDINE, SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE (STRAIN 8, TABLE 7).

	Colony counts.			
Hours:	0.	4.	24.	70.
Control	190	90	130,000?	>100,000,000
Neoarsphenamine, 1:150,000	190	50	600,000	>100,000,000
Sulfapyridine, 1:10,000	190	80	16	0
Sulfathiazole, 1:10,000	190	0	0	0
Sulfamethylthiazole, 1:10,000	190	300?	0	0

TABLE 7.—SUMMARY OF CHEMOTHERAPY ON DIFFERENT STRAINS OF *Strep. viridans* TESTED IN MARROW CULTURES.

Strains.	Sulfanilamide.	Sulfapyridine.	Sulfathiazole.	Sulfamethylthiazole.	Mapharsen.	Neoarsphenamine.	Neoarsphenamine plus sulfathiazole.
1	I	I					
2	I	I					
3*	...	...	...	...	...	S	
4	I	I	...	...	...	S	
5	...	III	III	I	IIII	SSSS	
6	...	SS	SSS	SS	I	SSI†	S
7	...	S	SSSS	SSS	E	EESE	S
8	...	S	S	S	...	I	
9	...	S	SESS	...	I	S	
10	...	SS	SS	...	I	E	
11	...	S	SE	SS	I	EE	

S, sterile; I, ineffective; E, effective (the colony counts were significantly lower than the counts in the control, or no organisms were found in the smears when the control was loaded).

* Strains 3 to 8 correspond to the strains represented in Tables 1 to 6 in the same order.

† I, larger inoculation.

In addition to the 7 experiments on 6 strains illustrated in the tables and figures 1 to 4 experiments were done on each of 5 other strains listed, and the results of all experiments on each of the strains tested are summarized in Table 7.* Sulfanilamide was ineffective

* Since this article was submitted for publication many other strains have been investigated, each of which responded to neoarsphenamine alone, sulfathiazole and sulfapyridine alone, or to all three drugs, and a few strains were found which responded to sulfanilamide.

against each of the 3 strains tested; mapharsen was effective against 1 of the 5 strains tested; sulfapyridine, against 6 of the 10 strains tested; sulfathiazole against 6 of the 7 strains tested; sulfamethylthiazole, against 4 of the 5 strains tested; and neoarsphenamine, against 8 of the 9 strains tested. Neoarsphenamine and sulfathiazole in combination were effective against both of the two strains tested. Since neoarsphenamine was effective when sulfathiazole was not and *vice versa* the combination would probably have been effective against each of the strains tested.

Comment. It is evident that sulfanilamide is relatively ineffective against the *Strep. viridans*. Sulfapyridine is effective against some strains but is ineffective against others. It appears to offer no advantage over the more soluble and probably less toxic drug, sulfathiazole. Sulfathiazole and sulfamethylthiazole in concentrations of 1:10,000 are effective against many strains of *Strep. viridans* and are ineffective against other strains. In marrow cultures sulfathiazole and sulfamethylthiazole in equal concentration are equally effective, but it seems probable because of the lesser toxicity and greater solubility and greater ease in securing adequate blood concentration that sulfathiazole will prove clinically superior. Mapharsen is effective against some strains in the lowest concentration of any drug tested. Neoarsphenamine is effective against more of the strains tested than any of the other drugs investigated, but a concentration of about 1:150,000 (or 6 parts per 1,000,000) must be maintained constantly over a period of 24 to 72 hours or longer.

The development of an accurate method for blood arsenic by Raulston, Magnuson and Chaney[9a,b] made possible the calculation of the laws governing the distribution of the drug in the body and its elimination from the blood in man.[6g] After a single dose the drug is distributed evenly through the blood volume, but rapidly leaves the blood and after 2 to 3 hours is distributed almost evenly throughout the body tissues. From this time on the blood level drops comparatively slowly. During both periods the drug leaves the blood by a clearance mechanism which corresponds to a clearance of about 50 cc. of blood per hour. To maintain continuously the blood level desired of 1 part in 150,000 (or 130 gamma of arsenic per 100 cc.), as the results are reported, one should give $\frac{1}{150{,}000}$ of the body weight in grams of neoarsphenamine $\left(\text{or } \frac{\text{body weight in kg.}}{150} = \frac{\text{body weight in pounds}}{330}\right)$ the first day, divided into 3 or 4 spaced doses. Each subsequent day for 3 to 6 days give three-fourths of the total dose given on the first day, divided into 3 spaced doses. For example: If the body weight is 60 kg., give a total of 0.4 gm. in divided doses of 0.1 gm. each at 8 A.M., 11 A.M., 2 P.M., and 8 P.M.

Every subsequent day give 0.1 gm. at 8 A.M., 3 P.M., and 10 P.M. On the third day and subsequently at intervals, just before giving the 8 A.M. injection, take blood for blood arsenic determination.[8,9] Adjust the doses up or down as necessary to keep the blood arsenic level between 100 and 130 gamma per 100 cc. when the blood is taken at this time.

In a 70-kg. (or 150-pound) patient, a dose of 0.1 gm. will raise the blood level about 400 gamma immediately after and about 30 gamma 2 to 8 hours after administration. This rise will be inversely proportional to the weight and directly proportional to the dose; for example, if the blood level in a 30-kg. patient is 50 gamma at 8 hours, 0.1 gm. of extra neoarsphenamine will raise the level to about 110 gamma 2 to 8 hours after the next dose.

If the clinical effectiveness of the drugs is similar to their effectiveness in marrow cultures, as seems probable from the high correlation between clinical results and our previous culture studies of the effectiveness of drugs against other organisms,[1,6a–c,e] the following treatment for subacute bacterial endocarditis should be investigated. Since simple bacteriologic culture methods of differentiating the organisms which respond well to both sulfathiazole and neoarsphenamine from those which respond to sulfathiazole or neoarsphenamine alone have not yet been developed, unless marrow culture studies are available, a trial of neoarsphenamine alone should be made first because of its more frequent effectiveness. Give neoarsphenamine as outlined previously to maintain a blood level of 130 gamma of arsenic per 100 cc. If the temperature is not normal by the fourth day, give enough sulfathiazole or sulfapyridine every 4 hours to maintain a concentration of 8 to 10 mg. per 100 cc. Discontinue the neoarsphenamine if there was no effect on the temperature, and continue both drugs if the neoarsphenamine alone had reduced the temperature but not to normal. Clinical trial of such therapy should be controlled by daily search for evidence of toxicity from the drugs and by daily leukocyte counts and frequent hemoglobin, arsenic and sulfathiazole or sulfapyridine determinations. It is evident that this therapy alone will carry a certain mortality, but it would seem justifiable to run these risks in a disease with the high mortality of subacute bacterial endocarditis. Such studies are in progress and will be reported in a later paper,[7] but not enough time has elapsed to draw final conclusions, although the results so far obtained have been encouraging.

Since it has not been determined which of these drugs is the most effective in penetrating vegetations or if any of them will be able to kill organisms in the depths of vegetations, it would seem desirable for the present at least to continue the administration of the drug over a long enough period of time so that there may be a chance for it to penetrate to the center of the vegetations or, in any event, for healing on the surface and sufficient scar tissue contraction to occur

to imprison any organisms that remain. How long this period of time is has not yet been determined. However, it would seem desirable if toxicity is not encountered to continue the therapy for 60 days or longer in repeated courses of 3 to 6 days separated by 3- to 6-day rest periods. In the use of heparin intravenously, as suggested by Friedman, Hamburger and Katz,[4] and by Kelson and White,[5] there is a considerable risk of cerebral hemorrhage, and at most it can only hope to prevent deposition of new platelets and fibrin on the surface. It seems logical to believe that if the organisms near the surface are killed such deposition will cease in any event. Clinical trial of this therapy without heparin is in progress and will be reported in a later paper.[8]

The failure of neoarsphenamine or other organic arsenicals to give clinical cures in the cases in which they have previously been tried[2] may be explained by the fact that our studies show that a uniform low concentration of about 1:150,000 must be maintained in the blood stream for 24 to 72 hours, and probably much longer, to reach the center of a vegetation or allow time for fibrous tissue contraction; whereas, these drugs have been given previously in single large doses as in the therapy of syphilis. Obviously, much further work needs to be done by the marrow culture method to determine whether any other arsenical preparation is superior to neoarsphenamine, and to determine whether these drugs will penetrate a clot or a vegetation removed at necropsy, as well as much controlled clinical investigation to determine what is the ideal frequency of administration and dose of each drug and whether heparin is essential too.

Summary. In marrow cultures sulfanilamide in concentrations of 1:10,000 is relatively ineffective against *Strep. viridans;* sulfapyridine, sulfathiazole and sulfamethylthiazole in concentrations of 1:10,000 are ineffective against some strains but lead to sterility with other strains. Neoarsphenamine in concentrations of 1:150,000 is effective against more strains than any of the other drugs tested, but is less effective than sulfathiazole or sulfapyridine against some strains. Mapharsen deserves further study; in a concentration of 1:1,500,000 it is effective against certain strains, but is not as uniformly effective as neoarsphenamine in concentrations of 1:150,000. Carefully controlled clinical studies of the effectiveness of sulfathiazole or sulfapyridine in a dosage sufficient to maintain a blood level of 10 mg. per 100 cc. with neoarsphenamine given in intermittent courses of small frequently repeated doses with the objective of maintaining a blood level of about 1:150,000 should be made, with and without heparin given by continuous intravenous drip. Such studies have given encouraging results to date, but several more months must elapse after therapy was discontinued before a final report will be justified. It is hoped that similar studies will be undertaken in other institutions equipped for thor-

oughly controlled studies of this nature. In making such studies the risk of arsenical poisoning, agranulocytosis and other toxic effects of sulfathiazole and of hemorrhage from the heparin therapy must be kept constantly in mind.

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QUICK'S PROTHROMBIN TEST SIMPLIFIED BY THE USE OF A STABLE THROMBOPLASTIN.

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Since Quick,[4] in 1935, introduced his prothrombin time test it has become widely used in the clinical investigation and control of the bleeding tendency of vitamin K deficiency which occurs in jaundice, hemorrhagic disease of the newborn, and other conditions.[5] The test measures the time taken for a sample of citrated plasma to coagulate, after recalcification, in the presence of an excess of tissue thromboplastin as compared with the time taken for a sample of normal citrated plasma to clot when treated in the same way. The test itself is extremely simple. The main reason that the practitioner

has difficulty in performing the test in his own laboratory is that it has heretofore been difficult to prepare the thromboplastin.

To perform the test as originally described by Quick, the thromboplastin is prepared from dried whole rabbit brain by saline extraction. The extract allows recalcified normal plasma to clot in 22 to 25 seconds, and retains its potency for about 4 days when kept at 5° C. In Quick's modification of his test,[3] the technique of which is the same and which is more commonly used at present, acetone-extracted brain substance is employed instead of dried whole rabbit brain. The saline extract prepared from acetone-extracted brain allows normal recalcified plasma to coagulate in 10 to 12 seconds and its activity begins to fall off 24 hours after its preparation.

Irrespective of which of these two thromboplastins is used, it is necessary to proceed with the rather laborious and time-consuming processes of removal and preparation of the brain, suspension, incubation and centrifugation of its saline extract. The necessity for having a high-powered centrifuge is alone sufficient to make the performance of the test impracticable for many whose office does not contain this piece of apparatus.

The introduction therefore of a stable thromboplastin requiring for its complete preparation no more than the addition of distilled water is desirable. This would greatly simplify the procedures involved in the carrying out of the Quick prothrombin test. At the suggestion of Dr. F. H. L. Taylor[7] we attempted the preparation of a stable thromboplastin by utilizing the method of "lyophilization" introduced by Flosdorf and Mudd.[1] A preliminary report of this preparation has been published.[6] The details of the preparation of such a stable thromboplastin suitable for general use in the Quick prothrombin test are presented below.

Methods. For reasons which will appear later, we preferred to use the original Quick procedure, using thromboplastin from dried whole rabbit brain.[4] Brains were removed from freshly-killed rabbits and the larger superficial blood-vessels stripped off after washing with water. The brains were then ground to a paste, spread thinly on a glass plate and thoroughly dried in an oven at 37° C. The dried residue was scraped off the plate and about 15 cc. of saline extract were prepared by adding 30 cc. of 0.85% sodium chloride solution to 3 gm. of dried brain, mixing with a glass rod and incubating at 56° C. for 15 minutes. On centrifuging the mixture at 2000 r.p.m. for 5 minutes, a somewhat opalescent supernatant fluid was obtained. About 2 cc. of this extract were set aside for testing as a control and the remainder placed in small serum bottles, 1 cc. in each. The contents of these bottles were then "lyophilized" and at the completion of the process the evacuated bottles were set aside for storage at room temperature (about 20° C.).

The portion of extract which was kept as a control was tested for thromboplastic activity by using it to determine the Quick prothrombin times of a series of dilutions of normal citrated plasma with prothrombin-free plasma prepared by the method of Kark and Lozner[2] so that the preparations contained 100%, 80%, 60%, 40%, 20% and 0% prothrombin (Table 1).

The technique used in the determination of these prothrombin times was essentially that of Quick.[4] One-tenth cubic centimeter of thromboplastin was pipetted into a tube 10 by 75 mm. and the tube placed in a constant temperature (37.8° C.) water-bath. After a few minutes 0.1 cc. of plasma was added and immediately thereafter 0.1 cc. of 0.277% solution of calcium chloride. At the moment of delivery of the calcium chloride solution from the pipette a stop-watch was started. The tube was agitated gently in the bath for 15 seconds and then rocked while held in the air until the contents ceased to flow freely. At this point the watch was stopped and the time taken.

Bottles containing the dry, powdered, "lyophilized" material were opened at intervals of 1, 2, 3, 4, and 10 weeks after "lyophilization" and the contents restored to their original volume by the addition of distilled water, when a somewhat opalescent solution was readily obtained. The thromboplastic activity was then determined on each occasion by testing against plasmas containing various percentages of prothrombin. At the same time the results obtained were compared with those given by an extract freshly made up from the original dried rabbit brain substance stored in the ice box at 5° C. The figures for these results are shown in Table 1.

TABLE 1.—THE QUICK PROTHROMBIN TIME OF MIXTURES OF NORMAL AND PROTHROMBIN-FREE PLASMAS USING FRESHLY PREPARED AND LYOPHILIZED THROMBOPLASTINS.

	Time in weeks after lyophilization of thromboplastin at which Quick prothrombin times were observed.	Quick prothrombin times of mixtures of normal plasma and prothrombin-free plasma (seconds). Percentage of normal plasma in mixtures.					
		100%.	80%.	60%.	40%.	20%.	0%.
Fresh thromboplastin extract for lyophilization . . .	Control	21	23	26	29	40	No clot
"Lyophilized" thromboplastin	1	21	24	27	32	50	"
Freshly prepared thromboplastin	1	20	21	23	28	42	"
"Lyophilized" thromboplastin	2	24	26	28	34	56	"
Freshly prepared thromboplastin	2	23	25	26	32	52	"
"Lyophilized" thromboplastin	3	23	25	28	34	54	"
Freshly prepared thromboplastin	3	21	23	25	29	45	"
"Lyophilized" thromboplastin	4	21	24	26	31	49	"
Freshly prepared thromboplastin	4	20	22	25	30	40	"
"Lyophilized" thromboplastin	10	21	23	25	33	68	"
Freshly prepared thromboplastin	10	21	23	26	33	68	"

Discussion. From Table 1 it will be seen that practically no loss of thromboplastic activity occurred in the process of "lyophilization" of the extract from dried whole rabbit brain and that storage of the evacuated bottles at room temperature over as long a period as 10 weeks caused no depreciation in potency. This is in contrast to the fresh saline extract of rabbit brain which retains potency for only a few days. Thus by this method an active thromboplastic material was obtained ready for immediate use on the addition of distilled water alone.

Availability of the thromboplastic substance in evacuated ampoules would seem to remove the one serious obstacle to the performance of the Quick prothrombin test in the physician's office and permits it to be performed with greater ease anywhere. The other reagents, sodium oxalate or citrate and calcium chloride are readily available; a water-bath at 37° C. can be improvised without

difficulty or indeed can be dispensed with entirely and the test carried out at room temperature provided that the patient's plasma and that of the normal control are treated identically. Enough dry thromboplastin for 9 tests is obtained by the "lyophilization" of a single cubic centimeter of saline extract from rabbit brain. To prepare from this dried material thromboplastin solution for immediate use in the test, all that is necessary is to add sufficient distilled water to make up the original volume.

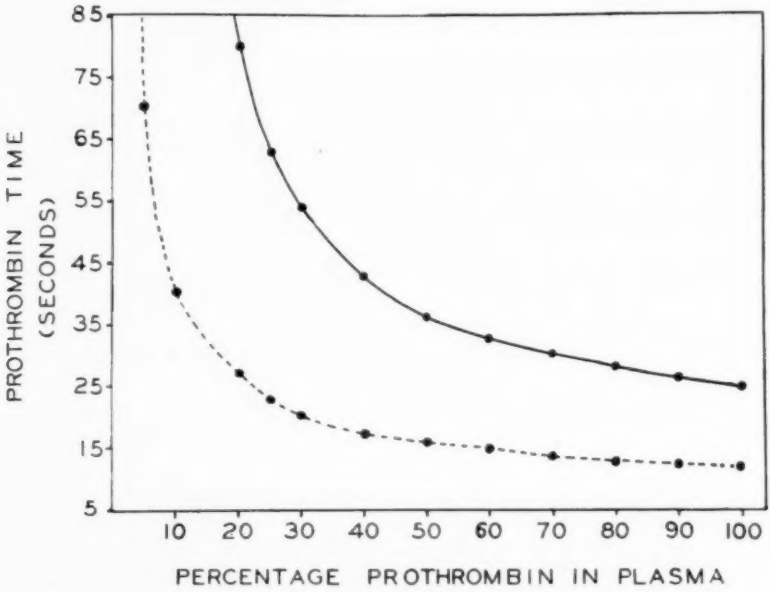

CHART 1.—The relation between the prothrombin percentage of human plasma and the Quick "prothrombin time" in the presence of Quick's original thromboplastin (solid line) and Quick's modified thromboplastin (broken lines).

The original test of Quick using thromboplastin from whole dried rabbit brain was employed in preference to his modification using thromboplastin from acetone-extracted brain. This is chiefly because of the extreme potency of the thromboplastic extract used in the latter modification of the test. So strong are its clot-accelerating powers that even with quite definite reduction in the blood prothrombin level only very slight prolongation of the prothrombin time occurs and it is not until dangerously low levels of prothrombin are reached that any marked change is noted in the prothrombin time.

A graphic comparison of the potencies of the two thromboplastic extracts derived from whole rabbit brain and acetone extracted

brain, respectively, is shown in Chart 1. In a test such as this, when the time of a reaction represents the concentration of one interacting substance, it is essential for accurate estimation of the amount of that substance present, that decrease in its concentration should be reflected by an appreciable prolongation of the time of the reaction. It is notable that a rise of 5 seconds in the prothrombin time when the first extract is used indicates a fall in prothrombin level to 70% of normal, while this amount of lengthening of the prothrombin time when the second extract is employed does not occur until the prothrombin concentration is as low as 50% of normal. When the "hemorrhagic level" (30% to 35% of normal) is reached the extract from dried whole rabbit brain permits a striking prolongation of prothrombin time (from 25 up to 50 seconds) while the more potent extract shows a rise only from 12 to about 18 seconds for an identical fall in the prothrombin level. It is therefore possible to make a more accurate estimation of the active prothrombin content of plasma by using the saline extract from dried whole rabbit brain, especially when the prothrombin concentration is reduced to a moderate degree, barely appreciable when the more potent extract is used. This is extremely important clinically, for instance, preoperatively in certain jaundiced patients, in whom a reduction of blood prothrombin to perhaps 70% of normal might pass unnoticed if the more potent thromboplastin were used, as it would be indicated by a prolongation of only 2 seconds in the prothrombin time over that of a normal control. If operation were carried out in such patients at this stage, without therapy with vitamin K, then a farther small drop in blood prothrombin as a result of operative procedures might well bring it to the hemorrhagic level with serious and possibly fatal results.

Summary. A method is described for the preparation of a stable thromboplastin suitable for use in the Quick prothrombin test. The material is ready for immediate use on the addition of distilled water alone, thus permitting of the performance of the test by the physician in his office, and allowing it to be carried out with greater ease anywhere.

Reasons are given for employing a relatively weak thromboplastin as prepared originally by Quick in preference to the potent thromboplastin which he introduced later.

The authors gratefully acknowledge the technical assistance of Nancy deFritsch, A.B.

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THE MECHANISM OF RENAL HYPERTENSION.

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The coexistence of arterial hypertension with pathologic changes in the kidneys has been known for a long time. Experimental studies indicated that hypertension could be produced by vascular alterations in the kidney, but increases in blood pressure were not consistent and of short duration. Systematic studies have only become possible with the discovery of Goldblatt, Lynch, Hanzal and Summerville,[9] that incomplete renal ischemia produces a marked and permanent arterial hypertension. This discovery has opened a new field in experimental studies, since the condition so caused in the dog and other animals is similar to human hypertension. It has thus been possible to prove the humoral mechanism of renal hypertension and to discover the presence of a pressor substance in the venous blood of ischemic kidneys. This substance can also be prepared *in vitro* and although its chemical constitution is still unknown its formation and mode of action have been studied. Our present knowledge of the mechanism of renal hypertension might be summarized as follows: Renal ischemia determines the secretion of "renin." This protein is an enzyme which acts on a blood globulin ("hypertensin precursor") and gives rise to a substance ("hypertensin") which produces vasoconstriction. Another enzyme "hypertensinase" which destroys hypertensin, is present in blood and tissues.

A. **The Presence of a Pressor Substance in Venous Blood of Ischemic Kidneys.** Experiments which prove that a pressor substance is secreted by ischemic kidney have been performed with: (*a*) kidneys from hypertensive dogs with chronic ischemia; (*b*) kidneys after complete ligation of the renal artery; and (*c*) kidneys after partial acute ischemia.

(*a*) Houssay and Fasciolo[16] found that if the ischemic kidney of a dog with chronic hypertension was grafted to the neck of a normal or nephrectomized dog, an increase in blood pressure was produced. This rise was prolonged and persisted for some time after the removal of the graft. It was more pronounced in nephrectomized than in normal dogs and not produced by grafting a normal kidney. Dicker,[4a] and Bouckaert, Grimson and Heymans[1] obtained

similar results. Houssay and Taquini[17] found that the citrated plasma obtained from the veins of ischemic kidneys produced vasoconstriction when perfused through a toad's hind limbs (Läwen-Trendelenburg preparation). Pressor activity has also been demonstrated in the systemic blood of hypertensive dogs. In the experiments of Solandt, Nassim and Cowan[28] an exchange transfusion of systemic blood was established between a hypertensive dog and a nephrectomized dog. A transient hypertension was observed in the latter.

(*b*) If after some hours of complete ischemia of normal kidneys the circulation is reëstablished a rise in blood pressure is observed in the same dog or in the recipient with the grafted kidney.[4b,27,30a,b] Vasoconstriction was observed when the citrated plasma was perfused through the Läwen-Trendelenburg preparation.[30b]

(*c*) Acute partial ischemia of a few minutes is sufficient to produce the appearance of a pressor and vasoconstrictor activity in the venous blood of normal kidneys.[2a,5,10,32]

The pressor activity of this blood was not modified by section of the vagi, denervation of the carotid sinus, adrenalectomy, or the injection of cocaine, atropine or Fourneau 933.[2b,3b] The vasoconstrictor activity of this blood was also revealed by the Läwen-Trendelenburg preparation or by the perfusion through denervated hind limbs of dogs.[2b,3b] It was found that the pressor substance of the venous blood of ischemic kidneys remained in solution after adding three volumes of acetone, that it was thermostable and insoluble in ether and amyl alcohol. Some of the chemical and pharmacologic properties of this substance were studied and as they did not correspond to any known pressor substance, it was named hypertensin.[3a,b,18]

It was later found[22] that hypertensin is formed in the blood. Ischemic kidneys secrete renin,[20,22] which acting upon blood globulins gives rise to hypertensin. If the venous blood of ischemic kidneys is collected in acetone or rapidly cooled no hypertensin is found in the extracts. It is found only after the blood has been incubated for a certain time. This generation of hypertensin is due to the action of renin as is shown in the following paragraph.

B. **Renin.** In 1898, Tigerstedt and Bergmann[31] discovered that kidney extracts contained a pressor substance: renin, which was not found in extracts of other organs. Subsequent studies[11,13,14,26] showed that the active substance was a protein, and probably a globulin inactivated by heat 60° C. The purification of renin has been lately studied by Swingle, Taylor, Collings and Ways.[29] A specimen that they kindly sent to us was found to be practically free from cathepsin and hypertensinase.[22]

The intravenous injection of renin produces a gradual rise in blood pressure which lasts from 10 to 30 minutes, depending on the dose. The effect is not modified by vagotomy, denervation of

the carotid sinus, pithing, or injection of atropine, cocaine or Fourneau 933. Nephrectomized dogs are more sensitive to renin,[35] and adrenalectomized and hypophysectomized rats are less sensitive.[33] Consecutive injections of large doses at short intervals produce each time a smaller response but the continuous injection of small amounts produces a sustained elevation of blood pressure.[15]

The pressure increase produced by renin is not direct but occurs by the intermediation of hypertensin. The perfusion of renin in Ringer solution through a vascular system: dog's tail,[21] or Läwen-Trendelenburg preparation,[35] does not produce vasoconstriction. If renin is diluted in citrated plasma or horse serum instead of Ringer's solution and perfused after short incubation, marked vasoconstriction results, due to the hypertensin formed. The plasma or serum must be previously tested alone, to discard any vasoconstrictor action ("Spätgift," vasoconstrictin).

The elevation of blood pressure has been generally used as a test for the activity of renin. The relation between blood pressure rise and dose has been studied by Swingle, Taylor, Collings and Ways.[29] The formation of hypertensin can also be used as a test. When renin is added to serum at 37° C. hypertensin is formed, as can be shown by testing the pressor action of the alcoholic extracts. With this method it is possible to detect quantities of renin 50 to 100 times smaller than by direct injection.

For instance, 2 cc. of one of our renin solutions were needed to increase the pressure of a 10 kg. dog by 30 mm. Hg. If 0.05 cc. of the same solution were incubated with 10 cc. blood globulins, the following pressure increases were obtained on injection of the extract to the same dog.

Time of incubation in minutes .	0	5	15	30	60
Pressure rise in mm. Hg . . .	10	24	34	52	54

However, this method can only be used with purified preparations because if hypertensinase is present, the hypertensin is destroyed.

There are several reasons for considering renin as an enzyme and blood globulins as the substrate. Renin is a protein and its activity is destroyed by heating. The yield of hypertensin is proportional to the amount of globulins. If the amount of renin exceeds the optimum, the maximum yield is not surpassed using 10 or 20 times more renin; the results obtained when a fixed amount of serum without hypertensinase is incubated with varying amounts of renin are shown in Figure 1. The maximum yield of hypertensin is attained in less than 15 minutes with 0.1 cc. and only in 2 hours with 0.05 cc. If the reaction were stoichiometric, the maximum amount of hypertensin formed ought to be proportional to the amount of renin.

Since the substrate on which renin acts is a protein and the reaction product is probably a polypeptide, it is reasonable to class renin

as a proteolytic enzyme. The pH optimum for the reaction was found to be between 7.5 and 8.5 (Fig. 2). The formation of hypertensin is not inhibited by cyanide, fluoride, octyl alcohol, thymol

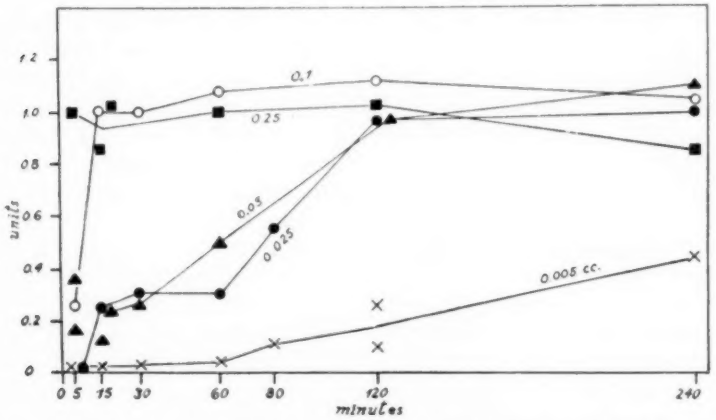

FIG. 1.—Units of hypertensin formed by incubating 10 cc. of bovine plasma—treated so as to destroy hypertensinase—with different amounts of renin solution during variable times. Temperature, 37° C. Hypertensin as estimated by comparing the pressure increases produced in chloralosed dogs with a standard solution. × 0.005 cc. renin, ● 0.025 cc. ▲ 0.05 cc. ○ 0.1 cc. ■ 0.25 cc.

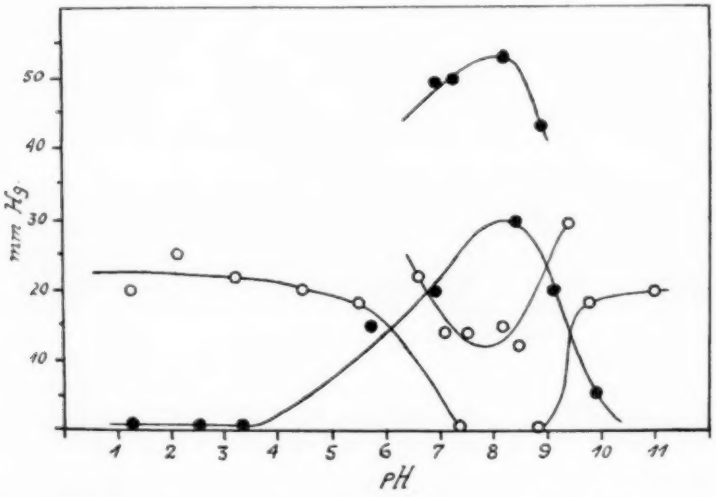

FIG. 2.—pH activity curve of renin and hypertensinase. Black dots: blood pressure increases produced by injecting the extract of 10 cc. blood globulin solution incubated with 0.25 cc. renin for 15 minutes. Each curve corresponds to one experiment. White dots: lower curve: extracts from 10 cc. ox-blood plasma incubated 80 minutes with 0.5 cc. hypertensin solution. Upper curve: another experiment with 50 minutes' incubation. Reaction temperature, 37° C. pH adjusted with HCl or NaOH and measured in an aliquot part with a glass electrode.

or toluol. Extracts of other organs (liver or spleen) do not produce hypertensin when incubated with blood globulins and other enzymes; pepsin, trypsin and papain were also found ineffective.

Renin is usually prepared from pigs' kidneys. This renin was found to be active on pig, ox, horse and dog serum, but no hypertensin was formed when it was incubated with human serum. On the other hand, renin prepared from human kidneys was active on any of these sera.[8] These results suggested that the injection of pig's renin would not produce a blood pressure increase in human subjects and this was found to be the case in the patients tested. The injection of human renin gives a pressure increase in human subjects (Battro and Lanari, unpublished results).

C. **Hypertensin Precursor.** The substance in blood serum on which renin acts to form hypertensin has been called hypertensin precursor or hypertensinogen. This is the substance which was found by Kohlstaedt, Helmer and Page[21] to produce vasoconstriction when mixed with renin. They call it renin-activator. However, as experiments indicate that it is the substrate of the enzyme renin, the name "renin-activator" does not appear to be desirable. It is precipitated from blood serum by half saturation with ammonium sulphate, by saturated sodium chloride at pH 2 to 3, potassium phosphate 2 M,[24] inactivated by heat and not precipitated by dialysis. Its properties correspond therefore to those of a pseudo-globulin.

Attempts to obtain it from other sources than blood serum have failed; liver, spleen, thymus, testes, lungs, heart or skeletal muscle, milk and egg proteins, hemoglobin, serum albumin and some vegetable proteins did not yield hypertensin when incubated with renin.

The hypertensin precursor can be estimated in blood samples by the maximum amount of hypertensin that it produces. It is necessary to use a renin preparation which is free from hypertensinase. This can be obtained by precipitating renin preparations with 25% NaCl at pH 2 to 2.5. Under these conditions hypertensinase is destroyed. In order to prevent the action of the hypertensinase of serum, the incubation period should be short (5 to 10 minutes) and therefore a large excess of renin is necessary.

The amount of renin to be employed was determined for each preparation as follows: 10 cc. of oxalated blood plasma (ox) were incubated at 37° C. with different amounts of renin during variable times. Three volumes of alcohol were added; after filtration and evaporation of the alcohol, the samples were injected into a chloralosed dog (Table 1). In this case 0.25 cc. was a sufficient amount of renin to produce the maximum yield of hypertensin in 5 minutes. After an incubation of 40 minutes, the hypertensinase in the plasma had destroyed all the hypertensin formed and no increase in blood pressure occurred. The pressure rises can be compared with those produced by a standard hypertensin solution.

TABLE 1.—RISE IN BLOOD PRESSURE FOLLOWING INTRAVENOUS INJECTIONS OF EXTRACTS OF BLOOD GLOBULINS INCUBATED WITH RENIN.

Cc. renin.	Increase of blood pressure in mm. Hg, time of incubation.		
	5 min.	15 min.	40 min.
0.25	20	22	
0.5	24	20	
1.0	20	14	
2.5	20	20	0

TABLE 2.—CHANGES IN HYPERTENSION PRECURSOR PRODUCED BY INTRAVENOUS INJECTION OF RENIN.

	Blood pressure increases in mm. Hg.							
Before renin	55	30	45	55	50	40	22	120
After renin	0	15	0	25	0	5	5	50

Samples of blood serum (7 to 18 cc.), taken before and 15 to 30 min. after injecting renin (0.5 to 1 cc. per kg.) into a dog, were incubated with an excess of renin for 10 minutes at 37° C. The alcoholic extracts were injected to a chloralosed dog. Each column records a different experiment.

Using this method some changes in the hypertensin precursor content of blood under different conditions were studied. After the injection of renin to chloralosed dogs, the hypertensin precursor decreases and even disappears from blood (Table 2 and Fig. 3).

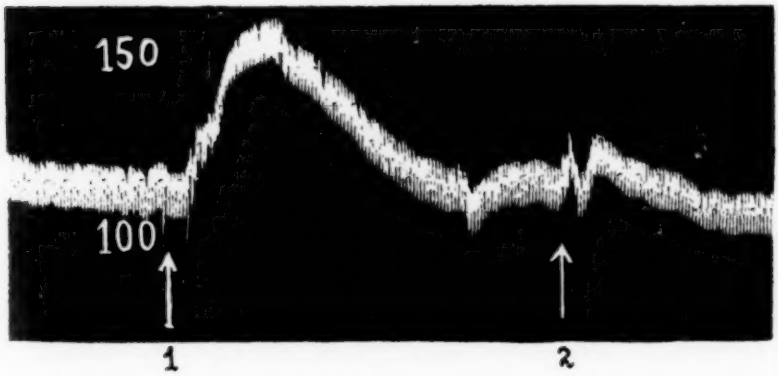

FIG. 3.—Hypertensin precursor in the blood of a 10 kg. dog before (1) and after (2) injection of 0.5 cc. renin per kg.; 10 cc. samples of serum incubated 10 minutes with an excess of renin. Rise in blood pressure observed by injection of alcoholic extracts to a chloralosed dog.

After nephrectomy, the hypertensin precursor increases. A sample of blood serum was obtained before and 48 hours after double nephrectomy in dogs. The precursor was estimated as described with the results shown in Table 3.

The increase in hypertensin precursor after nephrectomy may be explained by assuming that the kidney secretes normally small

amounts of renin which decompose some of the hypertensin precursor. It has also been found that there occurs a decrease in hypertensinase after nephrectomy (see below). The extent to which this change may affect the estimation of precursor has not been yet ascertained.

TABLE 3.—CHANGES IN HYPERTENSIN PRECURSOR PRODUCED BY NEPHRECTOMY IN DOGS.

	Rise in blood pressure, mm. Hg.					
Before nephrectomy	90	18	15	20	18	94
48 hours after nephrectomy . .	102	25	30	35	38	120

Samples of plasma were incubated with an excess of renin for 5 minutes at 37° C. and the extract tested for pressor activity in a chloralosed dog. Each column records 1 experiment.

D. **Hypertensin.** The incubation of renin with blood globulins gives rise to a pressor substance which has the same chemical and pharmacologic properties as the substance found in the venous blood of ischemic kidneys. This substance was named hypertensin.[3a,b,23] Experiments by Page and Helmer[24] led to the independent discovery of the same substance, which they named angiotonin. Page and Helmer report obtaining a crystalline picrate and oxalate. No melting point or elementary composition are mentioned.

Hypertensin is very soluble in water and soluble in glacial acetic acid, liquid phenol, ethylene glycol, only slightly soluble in absolute alcohol, insoluble in ether and butyl or amyl alcohol. It is resistant to acids (2 hours in HCl 1 n at 100° C.) but sensitive to alkali. It can be salted out by ammonium sulphate. It dialyzes through cellophane. It is inactivated by incubation with pepsin. Although Page and Helmer report that the biuret reaction is negative, the inactivation by pepsin (Fig. 4) would indicate that it is a polypeptide.

The method of preparation which we used was as follows: Dialyzed blood globulins were allowed to react with renin and then precipitated with three volumes of alcohol. The filtrate was evaporated *in vacuo* and extracted with ether. The solution was then either treated again with alcohol or dried, extracted with glacial acetic acid and precipitated with ether. Hypertensin can be extracted with phenol from aqueous solutions after saturating them with ammonium sulphate. The active substance can then be extracted by water after the addition of 2 volumes of ether.

A unit of hypertensin was regarded as the amount which gives a blood pressure increase of 20 to 30 mm. Hg in a 10 kg. chloralosed dog. About 1 unit is obtained from 10 cc. bovine serum. The blood pressure increase lasts 3 to 4 minutes and is roughly proportional to the amount injected, as was shown by Braun-Menendez, Fasciolo, Leloir and Muñoz.[3b]

Even after 15 to 20 injections, the injection of equal amounts produce equal effects; there is therefore no tachyphylaxis to hypertensin. The pressor action is not modified by previous injection of

Fourneau 933; it is reinforced by cocaine and specially by "veritol." Continuous injection of hypertensin (1 unit per minute) produces a sustained elevation similar to that produced by a single dose of renin. The pressor effect is not modified by double section of the vagi, pithing, adrenalectomy, denervation of the carotid sinus.[3a,b]

Hypertensin produces a marked vasoconstrictor action on the Läwen-Trendelenburg preparation (0.25 to 0.5 units in 100 cc. Ringer solution). A decrease in volume of the spleen and kidney was found after injection into the jugular vein of dogs. The heart rate was not modified in vagotomized dogs, in the heart lung preparation or in the isolated toad heart. Intravenous injection of hypertensin did not induce contraction of the retractor penis in pithed dogs; with high doses a slow contraction of the nictitating

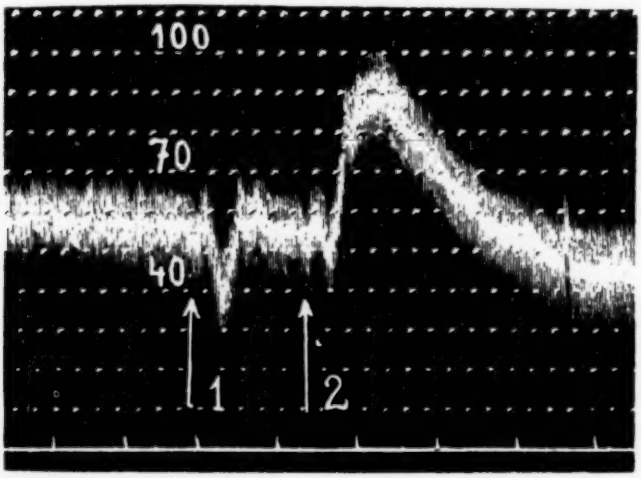

FIG. 4.—1, One unit of hypertensin incubated with pepsin at pH2. 2, The same with boiled pepsin solution. Alcoholic extracts injected to a chloralosed dog.

membrane was observed in chloralosed cats. In small doses (1 unit in 1000 cc. Ringer solution) it increased the height of contraction and the tonus of isolated rat or guinea pig uterus (which are inhibited by epinephrin), it stimulated contraction of rabbit uterus (as does epinephrin), it increased the tone of rat's gut (as does acetylcholine) and this action was not inhibited by atropine (Ludueña, unpublished results).

E. **Hypertensinase.** When blood serum is incubated with renin, the amount of hypertensin increases rapidly, then decreases and finally disappears.[3a,b,24] This disappearance is produced by serum and also by renin if impure preparations are used.

If 1 unit of hypertensin is incubated with 2 cc. of dog's serum (total volume, 2.5 cc.) at 37° C., the activity disappears gradually.

The pressure increases caused by the corresponding extracts were as follows:

Time of incubation in minutes . .	0	15	30	45	60	90
Pressure increases in mm. Hg . .	45	30	15	12	8	5

The hypertensinase of serum can be destroyed by incubating at 37° C. during 15 minutes, after adjusting the pH to 3.9. Under these conditions renin and hypertensin precursor remain unaltered. Impure renin solutions are highly active in destroying hypertensin as are also extracts of liver and spleen. Hypertensinase is destroyed by heating and has a pH optimum between 7.5 and 8.5 (Fig. 1). It can be therefore considered as an enzyme. The action is not suppressed by anaërobiosis, cyanide, octyl alcohol, chloroform and thymol.

Some measurements of hypertensinase activity of serum before and 48 hours after nephrectomy were carried out in dogs.

Samples of serum (1 to 2 cc.) were incubated 1 hour at 37° C. with 1 unit of hypertensin and the alcoholic extracts injected to chloralosed dogs. The pressure increase was compared with that produced by 1 unit of hypertensin. The differences per cent were as follows:

Before nephrectomy . . .	−34	−47	−20	−10	−89	−46
After nephrectomy . . .	+21	+15	+25	+10	−19	+ 8

These results show a clear decrease in the hypertensinase activity of blood after nephrectomy.

There are several observations which indicate that normal kidney exerts some sort of protective action against pressure increases produced by renal ischemia.[6a,b] If ischemia is produced in one kidney, the blood pressure increase is smaller when the other kidney remains intact. In many cases the pressure even returns to normal levels. When the artery of one kidney is compressed, it has often been observed that hypertension is produced only after the normal kidney is extirpated.[6a,7,19]

Some promising results have already been obtained in the treatment of experimental hypertension. Renin solutions when injected in large amounts sometimes produce a decrease in blood pressure. This effect can be interpreted as due to the fact that these solutions contain an antipressor substance. It has indeed been found that suitable kidney extracts can produce either a neutralization of the effect of renin,[12] or a decrease in pressure in hypertensive dogs.[25] Similar results on the hypertensive dog have been obtained in this laboratory, but the value of these experiments cannot yet be estimated. The antigenic properties of renin offer still another possibility and a beginning in this direction has been made by Johnson and Wakerlin,[18] who found that if a rabbit is repeatedly injected

with dog's renin, antibodies are formed so that the serum is capable of neutralizing the pressor effect of renin in the dog.

The better understanding of the mechanism of renal hypertension may give some indications as to the treatment of this disease. This should aim at: 1, suppressing or diminishing the secretion of renin by the kidney; 2, inhibiting the reaction of renin with blood globulin; 3, diminishing the amount of hypertensin precursor; 4, inhibiting the action of hypertensin by increasing the amount or the activity of hypertensinase or some other neutralizing agent.

Summary. The ischemic kidney secretes renin. This substance is an enzyme which acts on a blood globulin ("hypertensin precursor") and gives rise to a substance ("hypertensin") which has a direct vasoconstrictor action. Another enzyme "hypertensinase," which destroys hypertensin, is present in blood and tissues.

Hypertensin has been found in the blood of ischemic kidneys and can also be prepared *in vitro* by incubating renin with blood globulins. Some chemical and pharmacologic properties of hypertensin have been studied.

Methods are described for the estimation of renin, hypertensin precursor and hypertensinase in blood.

After injection of renin into chloralosed dogs, the hypertensin precursor decreases and even disappears from the blood. After nephrectomy, the hypertensin precursor increases and hypertensinase decreases.

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CLINICAL EXPERIENCE WITH SULFAMETHYLTHIAZOLE.*†

[2 (PARA-AMINO-BENZENE-SULFAMIDO) 4-METHYLTHIAZOLE.]

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We have previously submitted a preliminary report[1] on the use of sulfamethylthiazole for several patients, one of whom recovered from septicemia, the etiologic agent of which was *Staphylococcus aureus*. Subsequently, there has appeared a brief clinical report on the use of this drug by Carroll and associates.[4] The thiazole derivatives of sulfanilamide, 2-sulfamidomethylthiazole, 2-sulfamido-4-methylthiazole and 2 sulfamido-4-phenylthiazole, have also been the subject of a preliminary report of the Council on Pharmacology and Chemistry of the American Medical Association and of a recent editorial in the journal of that Association.[7] We believe that the subject of sulfamethylthiazole is of sufficient importance to warrant a statement of our clinical experience with this drug to date.

The compound, sulfanilamide, has thus far formed the basis for a related group of therapeutically active substances. Efforts to produce a drug with greater therapeutic effect and with less toxicity have led to the production of many compounds only a few of which have been adaptable for clinical purposes. Of the various sulfonamide drugs in use at present, neoprontosil seems to possess less toxicity than sulfanilamide, but its therapeutic effect on the *Strep. hemolyticus* also appears to be somewhat less. Sulfapyridine is effective against the *Strep. hemolyticus* but has proved to be of particular value in the treatment of infections due to the *Dipl. pneumoniæ*. In addition, sulfapyridine to date, when administered orally or intravenously as the sodium salt of sulfapyridine, in amounts sufficient to produce a high concentration of the drug in the blood, has thus far appeared to be the most useful drug in the treatment

* The authors wish to acknowledge the coöperation of the medical research division of the Winthrop Chemical Company in furnishing quantities of this drug for the study described herein.

† Submitted for publication June 10, 1940.

of infections due to the *Staph. aureus*. However, the use of sulfapyridine has been attended frequently by certain troublesome and dangerous manifestations of toxicity. These manifestations have included all of the toxic effects of sulfanilamide plus an increased tendency toward the occurrence of gastro-intestinal upsets such as nausea and vomiting. These latter effects although possibly due to some local irritative action may also be central in origin, for they are experienced by patients receiving only the sodium salt of sulfapyridine by the intravenous route. Renal complications due to the precipitation of acetylsulfapyridine crystals in the tubules and pelvis of the kidney are also known to occur. The subject of these latter changes has recently been reviewed by Plummer and McLellan[15] who stated that they may vary from simple calculous ureteritis and pyelitis that produces hematuria to severe pyelonephritis that results in renal insufficiency and azotemia. Experience has shown that any of these complications may make the problem of sulfamido therapy a difficult one at times.

In a search for some other compound which might afford a solution to some of these problems, we have previously used sulfanilyldimethyl-sulfanilamide (di-septal, ulinon) and have reported on our experience[9] with it and on our discarding of it.

Certainly any new compound which may be presented on a basis of experimental study that indicates lessened toxicity and increased therapeutic efficiency over other available compounds against the *Staph. aureus* warrants a thorough clinical trial. It must be borne in mind, however, that past experience has indicated a definite difference between toxic effects as exemplified by animal experiments on the one hand and the response of human beings on the other.

In August, 1939, Fosbinder and Walter[8] found that heterocyclic amino compounds other than 2-aminopyridine might be coupled with the sulfanilyl radical without great change in physiologic activity. In summary, they stated that the thiazole compounds appeared to possess activity comparable to that of sulfanilamide and sulfapyridine.

Following this, there appeared in November, 1939, simultaneous reports by van Dyke, McKee, and associates,[6,14] and by Cooper[5] and associates on animal experiments with the thiazole compounds. The former group working only with sulfathiazole reported favorably on its use. Cooper and his associates found that sulfathiazole and sulfamethylthiazole were equal to sulfanilamide in therapeutic effect but were slightly inferior to sulfapyridine when orally administered in the treatment of streptococcal and Type II pneumococcal infections in mice. They did not take into consideration, as Long and Bliss[12] have pointed out, that an adequate concentration of the thiazole compounds in the blood may not have been present due to the rapid absorption and elimination of these drugs on oral adminis-

tration. Rake and associates[16] have reported that the chronic toxicity of sulfathiazole for mice was greater than that of sulfapyridine but that the latter compound was more toxic in rats and monkeys.

In December, 1939, Barlow and Homburger[2a] reported on studies of sulfathiazole, sulfamethylthiazole, and sulfaphenylthiazole. They concluded from the treatment of experimental infections with *Staph. aureus* in mice that sulfathiazole and sulfamethylthiazole were superior to sulfapyridine in their therapeutic actions on these infections. They found that in a significant number of mice treated with the thiazole compounds, the kidneys, prostate gland, liver and spleen were essentially normal save for a few scars from healed abscesses. Later[2b] they demonstrated in experimental infections in mice that the chemotherapeutic effects of sulfathiazole and sulfamethylthiazole were superior to those of sulfanilamide and were equal to those of sulfapyridine in infections due to *Beta* hemolytic streptococci and due to pneumococci, Types I, II, and III. From experiments for tolerance of single doses and also for chronic tolerance of the sodium compounds of sulfamethylthiazole and sulfapyridine, they found that the latter preparation was more toxic than sulfamethylthiazole. They concluded that on the basis of this superior margin of safety, sulfathiazole and particularly sulfamethylthiazole appeared favorable when compared with sulfanilamide and sulfapyridine.

Lawrence[10] reported, following experiments on broth cultures, that the three thiazole compounds, sulfathiazole, sulfamethylthiazole, and sulfaphenylthiazole, were superior to sulfanilamide and sulfapyridine in their bacteriostatic effects on pneumococci, Types I, II and III, *Beta* hemolytic streptococci, gonococci and the *Staph. aureus*.

Long and Bliss[12] have concluded that sulfathiazole is as effective a bacteriostatic agent as sulfapyridine in broth cultures of certain strains of Lancefield's Groups A, D, and G, *Beta* hemolytic streptococci, *Escherichia coli*, *Staph. aureus*, pneumococci, Types I and II, and *Proteus vulgaris*. Sulfathiazole was slightly less effective than sulfapyridine in controlling experimental pneumococcal infections in mice, probably due to the more rapid absorption and excretion of the former drug.

Long, Haviland, and co-workers[13] recently reported, after experimental studies with sodium salts in mice, that sulfathiazole had a lower toxicity than sulfapyridine, but that addition of the methyl group increased its toxicity 50%, and that the latter preparation was therefore more toxic than sulfathiazole or sulfapyridine.

On the basis of these early reports, particularly of Barlow and Homburger,[2a,b] which indicated that sulfamethylthiazole was particularly effective against staphylococcal infections and possessed a low toxicity, we began the use of this drug orally in certain selected cases at The Mayo Clinic. We attempted primarily to treat patients

who had infections produced by staphylococci and pneumococci, but we also used the drug against infections caused by organisms other than staphylococci and pneumococci or against infections of unknown etiology in an endeavor to gain information regarding its action. We realize, of course, that it is not possible to draw entirely accurate conclusions from the study of a small group of cases such as is presented herein; nevertheless, we believe that the study will allow certain tentative and some definite conclusions to be made regarding the therapeutic action of the drug and its toxicity.

We are reporting at this time on the use of sulfamethylthiazole in the treatment of 106 patients at The Mayo Clinic. For purposes of simplification, we have roughly classified the infections encountered as follows: pneumonia, 30 cases; septicemia, 7 cases; subacute bacterial endocarditis, 5 cases; pelvic infections, 5 cases; infections of bone, 4 cases; cutaneous infections, 25 cases; infections of the ear, nose and throat, 13 cases; urinary infections, 3 cases;* and miscellaneous, 14 cases. The organisms identified in these various cases were: *Diplococcus pneumoniæ* in 7, *Strep. hemolyticus* in 7, *Staph. aureus* in 31, *Strep. viridans* in 6, *Strep. anærobicus* in 1, *Escherichia coli* in 1, *Strep. fæcalis* in 1, and *Klebsiella pneumoniæ* in 1.

In the treatment of all of these patients, the doses of sulfamethylthiazole employed in general were similar to those which we have given when using other sulfamido drugs. The doses averaged from 4 to 6 gm. daily for adults with moderate infections, to as high as 13 gm. daily for adults with septicemia and subacute bacterial endocarditis. The general policy toward adults with severe infections such as septicemia was to give 4 to 5 gm. as an initial dose and to follow this by 1 to 1.5 gm. every 4 hours as a maintenance dose. In the event that a satisfactory result was not obtained or the concentration of the drug in the blood was low, these doses were increased to as much as 2 gm. every 4 hours for periods of 4 and 5 days. For adults with infections of moderate degree, the general procedure was to give 4 to 6 gm. daily in 5 or 6 divided doses. In several of these cases, when it seemed impossible to obtain a satisfactory concentration of the drug in the blood by oral therapy, the sodium salt of sulfamethylthiazole was given intravenously.

Sodium sulfamethylthiazole was obtained by adding sodium hydroxide to sulfamethylthiazole in equal molecular proportions; the molecular weight of sulfamethylthiazole is 269 and that of sodium hydroxide is 40. A 10% solution of sodium sulfamethylthiazole in distilled water was then prepared, and the pH of the solution was brought to approximately 10.4 by adding 3.7 cc. of normal sodium hydroxide. As with a solution of the sodium salt of sulfapyridine, this marked alkalinity made it necessary to avoid injection of any material into subcutaneous tissue. Approximately 1.5 gm. or 30 cc.

* This does not include patients treated with sulfamethylthiazole in the Section on Urology.

of a 10% solution of sodium sulfamethylthiazole (not more than 50 mg. per kilogram of body weight) was given slowly intravenously as a single dose and the dose was repeated in 3 to 4 hours if necessary. This 10% solution of sodium sulfamethylthiazole in distilled water was also given in amounts up to 2.5 gm. in 1 liter of 5% solution of glucose. We noted no untoward effects from the use of this form of treatment and found that we were able to produce the desired concentrations of the drug in the blood. When an attempt was made to give 5 gm. of the 10% solution of sodium sulfamethylthiazole in 1000 cc. of a 5% solution of glucose, crystallization of the solution occurred within 12 hours and was not affected by heating.

The concentrations of the drug in the blood were estimated by A. E. Osterberg according to the method for sulfanilamide by Bratton and Marshall,[3] but a standard prepared from sulfamethylthiazole instead of from sulfanilamide was employed. Observations on these concentrations indicated that the values for sulfamethylthiazole in the blood were inclined to follow those levels of sulfapyridine obtained when the latter drug was given but were slightly lower. Frequently it seemed impossible to maintain adequate concentrations of the drug even when increased amounts were given orally. On average oral doses of 4 to 6 gm. daily, concentrations of the free drug in the blood varied from less than 1 mg. to 9 mg. per 100 cc. and the majority of values ranged between 3 and 4 mg. per 100 cc. The highest concentrations encountered ranged in a few instances from 10.2 to 15.4 mg. per 100 cc. in patients who received 11 to 13 gm. of the drug daily. Of striking interest was the fact that the values for the conjugated drug in the blood were quite low at all times and that the concentration of the free drug closely approximated the total concentration in each instance. It seemed possible that, whereas total values for sulfapyridine might run higher on comparative drug doses, the free values of sulfamethylthiazole more closely approximated those of free sulfapyridine. Illustrated representative values for comparative total and free concentrations of sulfamethylthiazole in mg. per 100 cc. of blood are as follows: free 1.0 and total 2.3; free 2.2 and total 2.8; free 7.4 and total 10.4. The pattern of high concentrations of the drug in the urine as seen with sulfanilamide and sulfapyridine was also followed. On average doses of 4 to 6 gm. of sulfamethylthiazole daily, representative concentrations of the drug in mg. per 100 cc. of urine were as follows: free 130 and total 215; free 195 and total 195; free 67.5 and total 185.

With the exception of the extremely significant and important complication, lower motor neurone involvement, which occurred in 3 cases, we were impressed by the general lack of common toxic manifestations produced by sulfamethylthiazole. Anorexia, nausea, or mild emesis were the toxic symptoms most frequently encountered, but their occurrence was much less than we have noted with the use of sulfapyridine. Of the 101 patients treated, there were 20 with

anorexia, nausea, or emesis. Of these patients 15 had mild symptoms, 2 had symptoms of a moderate degree and 3 had severe symptoms. Of these 20 patients with anorexia, nausea, or emesis, there were 2 who had had previous similar symptoms to the point of intolerance with the use of sulfapyridine. There were also 7 patients in this group who had marked nausea and emesis when sulfapyridine was used previously but who had no similar symptoms when they were subsequently given sulfamethylthiazole. In only 3 instances were these symptoms of sufficient degree to necessitate discontinuing treatment.

The toxic effect of sulfamethylthiazole which occurred next in frequency was a cutaneous eruption which 9 patients experienced. All of these lesions were of a maculopapular urticarial type and were accompanied by mild pruritus and, at times, by a fever of 99 to 100° F. (37.2 to 37.7° C.). The eruption tended to occur mostly on the upper part of the trunk but it also involved the neck, abdomen and extremities. In each instance it appeared between the seventh and tenth days of treatment and disappeared promptly within 20 to 30 hours after administration of the drug was discontinued.

In none of the patients treated was there any evidence of a change in the number of leukocytes suggestive of leukopenia or agranulocytopenia, and only 1 patient had a significant decrease in the number of erythrocytes. This patient had chronic uveitis and had received a total of 45 gm. of sulfamethylthiazole. The number of erythrocytes per cubic millimeter of blood progressively decreased from 4,780,000 to 3,470,000 during the sixth to ninth days of treatment and then remained stationary after administration of the drug was discontinued. There seemed to be no tendency for the drug to cause a decrease in the carbon dioxide-combining power of the blood. There was no evidence of pyelonephritis or involvement of the urinary tract of any of these patients save one who received sodium sulfamethylthiazole intravenously and who had a concentration of 20.2 mg. of the drug per 100 cc. of blood. This patient had *Staph. aureus* septicemia, and the case (Case 4) is considered in detail later in this discourse. Cyanosis was questionably discernible in only 3 cases, and in none was there found any significant amount of methemoglobin or sulfmethemoglobin by spectroscopic methods.

The most important complication encountered was lower motor neurone involvement, a condition which offers a real contraindication to indiscriminate use of sulfamethylthiazole. We believe that this condition is more accurately described by the term "lower motor neurone involvement" giving rise to muscle weakness than by the term "peripheral neuritis," as the disturbances present were not of a sensory nature but were of the nature of a pure motor weakness. The lesions which occurred showed an absence of muscle tenderness and presented no loss of pain, touch or temperature sensation. The occurrence of this complication served as a reminder of previous

experiences with sulfanilyl dimethyl sulfanilamide. Appearing as it did, after an experience with sulfamethylthiazole used in varying doses for approximately 100 patients, it again illustrated the fallacy of a general interpretation of the results of experiments on toxicity of the drug for animals when these results are applied to man. It is of interest in this regard that, in general, experiments on animals showed the toxicity of this drug to be quite low.

Long's[11] studies have recently indicated that the addition of phenyl or methyl groups to the thiazole compounds might increase their toxicity. No physiologic explanation for the occurrence of this complication with certain sulfamido compounds has yet been found. One of these patients had serious, chronic systemic disease complicated by pneumonia, empyema and repeated hemorrhage. There had previously been used 13.5 gm. of sulfanilamide and 13 gm. of sulfapyridine. The patient was intolerant to these drugs, and subsequently 17 gm. of sulfamethylthiazole were given in a 3-day period, 43.5 gm. in an 8-day period 1 month later, and 19 gm. in a 4-day period several days later. We judged the drug to have been of marked value to this patient. Lower motor neurone involvement as evidenced by bilateral foot-drop was noted some time after the administration of sulfamethylthiazole had been discontinued. The rôle of sulfamethylthiazole is not definite here and the weakened general condition of this patient may have been a definite factor in the production of this complication. The other 2 patients who experienced this condition were ambulant. In 1 instance, 38 gm. of the drug had been given in a period of 7 days, and in the other, 71 gm. had been given in 13 days. Both of these patients had chronic disease that had been resistant to previous treatment and the drug appeared to be of definite benefit. In each patient, foot-drop appeared bilaterally between 1 and 2 weeks after administration of the drug was stopped. In addition, 1 patient had mild weakness of the forefinger and thumb of both hands. Pain in the calves of the legs immediately preceded the onset of foot-drop. All of these patients have made definite and marked improvement (graded 75%) with regard to the lower motor neurone involvement. Vitamin B_1 has been given to all.

Of the total of 106 patients, there were 30 with pneumonia, and of these, 27 had bronchopneumonia and 3 had lobar pneumonia (Table 1). There were no deaths among the 27 who had bronchopneumonia, and the results were considered good in 13 cases and poor in 14. Of the 13 patients who obtained good results, the temperature became normal on the first day after treatment in 2, and on the fourth day in 2. The rapidity of response to therapy in these 4 cases was such as to suggest the presence of lobar pneumonia, but pneumococci were not found in the sputum. In 12 of these 13 cases in which the results were graded good, the temperature became normal in 8 days, and in the other, the temperature was

normal on the tenth day. The results were recorded as poor in 14 cases because fever persisted for more than 10 days, even though some significant lowering of fever and general improvement occurred in some after use of the drug. In these 14 cases, empyema occurred in 2, pleural effusion in 2 and serious preëxisting systemic complications were present in 3. Excellent and striking results were obtained by the 3 patients who had lobar pneumonia (Type I pneumococcus), and in each of these instances, the temperature promptly fell to

TABLE 1.—SUMMARY OF EXPERIENCE WITH 30 CASES OF PNEUMONIA, IN WHICH SULFAMETHYLTHIAZOLE WAS EMPLOYED.

	Bronchopneumonia.	*Lobar pneumonia.*
No. of patients	27: 14 males, 13 females	3: 2 males, 1 female
Range of ages, years	2 to 78	2 to 7
Average age, years	42.6	4.0
Extent of pulmonary involvement	1 lobe, 14 cases; 2 lobes, 13 cases	1 lobe, 4 cases
Postoperative complication	8 cases	None
Range of treatment, days	3 to 21	7 to 8
Average dur. of treatment, days	7	7.7
Average dose of sulfamethylthiazole per course of treatment, gm.	30.2	22.1
Average daily dose of sulfamethylthiazole, gm.	4.0	2.8
Supplementary intravenous use of sodium salt	2 cases	None
No. of days of treatment that preceded normal temperature	*Days* — *Cases*: 1 — 2; 2 — 2; 4 — 2; 5 — 1; 6 — 2; 8 — 3; 10 — 1; 10+ — 14	*Days* — *Cases*: 1 — 3
Results	Good, 13 cases (48.1%) Poor, 14 cases (51.8%)	Good, 3 cases (100%)
Complication of empyema	2 cases	None
Organisms cultured from sputum	*Strep. hemolyticus*, 1 case *Strep. viridans*, 1 case *Staph. aureus*, 1 case *Diplococcus pneumoniæ*, Type VI, 1 case *Diplococcus pneumoniæ*, Type XVI, 1 case *Diplococcus pneumoniæ*, Group E, 1 case Unidentified, 12 cases	*Diplococcus pneumoniæ*, Type I, 3 cases
Reactions from sulfamethylthiazole	Mild anorexia, nausea and emesis, 2 cases Marked anorexia, nausea and emesis, 1 case Exanthem, 3 cases Lower motor neurone involvement, 1 case None, 20 cases (74%)	None, 3 (100%)
Previous reaction to sulfapyridine and no reaction to sulfamethylthiazole	3 cases	None
Range of concentration of sulfamethylthiazole in the blood, mg. per 100 cc.	1 to 12.2	1 to 4.2
Average concentration of sulfamethylthiazole in the blood, mg. per 100 cc.	3.2	1.3

normal within a period of 24 hours. Temperature charts of these 3 patients are shown in Figure 1*a*, *b*, and *c*. In treating patients who had pneumonia, the general tendency was to give two successive doses of sulfamethylthiazole of 2 gm. each at intervals of 4 hours to adults and then to continue with 1 gm. every 4 hours. More detailed data regarding these patients may be obtained from Table 1.

A group of 6 patients with *Staph. aureus* septicemia were treated with sulfamethylthiazole. Of these, 3 were men and 3 were women,

and their ages ranged from 23 to 62 years. Sulfapyridine had been administered to 2 of these patients preceding the use of sulfamethylthiazole and its administration was discontinued because of severe nausea and emesis. Sulfamethylthiazole was well tolerated by these 2 patients. The initial blood culture in all but one of these cases showed 100 or more colonies of organisms per cubic centimeter of blood. Four of these patients died and 2 recovered. All of the cases in which death occurred are of sufficient interest to warrant being briefly reported.

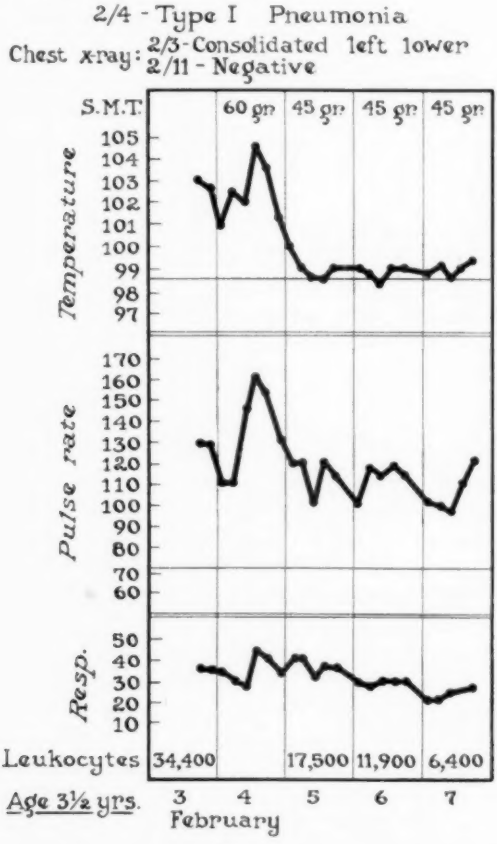

FIG. 1a.

Case Reports. CASE 1.—A man aged 58 had a septic fever to 104° F. (40° C.) 3 days after a transurethral prostatic resection and had been treated with 16 gm. of sulfanilamide over a period of 6 days because of infection in the urinary tract. Chills and fever had been present for 13 days, and a culture showed 200 colonies of organisms per cubic centimeter of blood 3 days before treatment with sulfamethylthiazole was started. This patient was given 23 gm. of the drug orally in 3 days, and at the end of this time, a culture

showed a reduction to 80 colonies of organisms per cubic centimeter of blood. The concentration of the drug in the blood reached 6.6 mg. per 100 cc. At this time, a cerebrovascular lesion developed with a left hemiplegia and chemotherapy was discontinued. Postmortem examination showed infarcts in the brain and ulcerative endocarditis.

Case 2.—A man, aged forty-eight,* had been acutely ill for a week. A culture gave evidence of "innumerable organisms" per cubic centimeter of

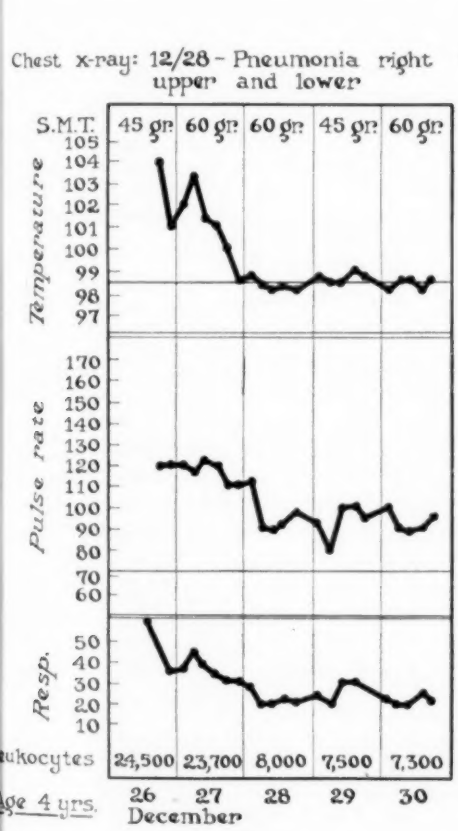

Fig. 1b.

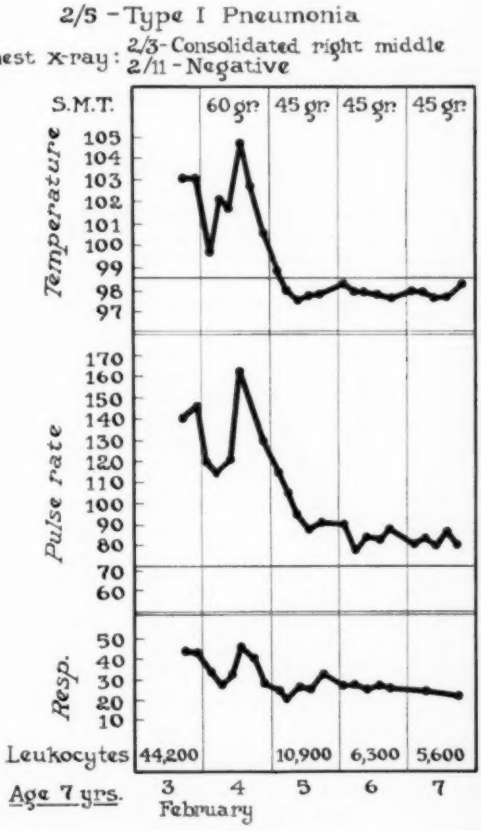

Fig. 1c.

Fig. 1a, *b* and *c*.—Temperature, pulse and respiration in 3 cases of lobar pneumonia, treated with sulfamethylthiazole.

blood for 2 days preceding sulfamethylthiazole therapy. Neoprontosil and sulfapyridine had been given previously. This patient received 54.5 gm. of sulfamethylthiazole orally in 6 days without improvement. No determinations of concentrations of the drug in the blood were made. Postmortem examination showed metastatic miliary abscesses of the lungs and kidneys and acute splenitis.

* This patient was seen in consultation through the courtesy of Drs. Lepak and Scott of St. Paul.

CASE 3.—A woman, aged 62, was treated 3 days after the onset of fever and chills and 1 day after a culture with 300 organisms per cubic centimeter of blood was obtained. She was given 88.5 gm. of sulfamethylthiazole in 8 days without benefit. A concentration of 10.4 mg. of the drug per 100 cc. of blood was obtained. Postmortem examination revealed ulcerative endocarditis with abscesses of the lungs, liver and kidneys, and a terminal bilateral bronchopneumonia.

CASE 4.—This case was of particular interest. This patient, a woman of 45, was in a state of severe inanition as the result of chronic tuberculous endometritis and salpingitis. She had in addition, a widespread exfoliating cutaneous lesion suggestive of pemphigus foliaceus. Anorexia and vomiting had existed for some time, and it proved impossible after trial of sulfamethylthiazole orally for 3 days to obtain a concentration of the drug in the blood greater than 2.3 mg. per 100 cc. Subsequently, the drug was administered solely by intravenous methods for a period of 8 days and during this time the patient was sustained entirely by intravenous fluids. The concentration of the free drug in the blood was maintained between 12 and 20 mg. per 100 cc. At the later point there was a temporary suppression of urine which disappeared in 24 hours when the concentration in the blood was lowered to 12 mg. per 100 cc. No significant changes occurred in the number of erythrocytes or leukocytes. Definite clinical improvement occurred and the temperature became approximately normal. The number of colonies of organisms per cubic centimeter of blood progressively decreased as follows: 100, 50, 50, 6, 4, and 2. The last culture was obtained in the final 24-hour period of life. Death appeared due to inanition rather than to sepsis. Of special interest is the fact that, at necropsy, no abscesses were found in the liver, kidneys or lungs. There was a considerable accumulation of acetylsulfamethylthiazole crystals in the pelvis of each kidney, but these accumulations had not seemed to interfere with the excretion of urine.

All patients who have staphylococcal septicemia present a grave aspect, and we should feel that the prognosis under similar conditions to those which prevailed in the aforementioned cases seems hopeless.

Of the 2 cases in which recovery occurred, 1 has been previously reported. The other was that of a man who had pneumonia and who on two successive occasions was found to have 30 and 25 colonies of organisms, respectively, per cubic centimeter of blood. This patient made a rapid recovery following oral administration of the drug.

One patient, a man of 59, had a *Klebsiella pneumoniæ* septicemia. He had been acutely ill for many months with this condition and had failed to respond to intensive treatment with sulfanilamide and sulfapyridine. He was treated with large doses of sulfamethylthiazole (78 gm. in 8 days) just preceding death, but the course of the disease remained unaltered.

Five patients with subacute bacterial endocarditis were treated with sulfamethylthiazole; the total amounts varied from 38 to 214 gm. over periods of 6 to 26 days. In each case there occurred some decrease in the number of colonies of *Strep. viridans* per cubic centimeter of blood, and in 3, temporarily, the culture resulted in no growth. In spite of some mild temporary improvement in symptoms, the disease was fundamentally unaffected by treatment which we considered a failure in each instance.

In 5 cases of pelvic inflammatory disease not of gonococcal origin sulfamethylthiazole was used in treatment. In 3 of these cases, this lesion was secondary to carcinoma of the cervix. In 1 instance the result was good, in another fair and in another poor. In another case in which carcinoma of the rectum and an associated pelvic abscess were present anaerobic streptococci were cultured from the abscess, and the disease was treated in its terminal stages but death occurred. In all of the other cases, the causative organism was not identified. The fifth case was one in which an acute inflammatory pelvic lesion was present which responded promptly to sulfamethylthiazole.

Four patients with osteomyelitis were treated with sulfamethylthiazole. One of these patients had multiple sinuses from a chronic paravertebral abscess and his condition was unimproved after he received 36 gm. of the drug in 9 days. In 2 other cases, the *Staph. aureus* was found in pus from draining abscesses. In 1 of these cases, the temperature became normal on the fifth day of treatment, and in the other, on the twelfth day of treatment; in the latter case, one aspiration was made from the abscess. In the fourth case, a recurrent osteomyelitis of the right femur was present from which the *Staph. albus* had previously been recovered. The temperature became normal and recovery occurred after he had received 25 gm. of sulfamethylthiazole.

There were 25 patients with various types of infections that involved the skin and subcutaneous tissues. Significant data concerning these patients are grouped in Table 2.

TABLE 2.—SULFAMETHYLTHIAZOLE THERAPY IN CUTANEOUS INFECTIONS.

	No. of patients.	Organism isolated from lesion.	Results.	Average total dose of drug, gm.	Average no. of days of medication.	Average daily dose of drug, gm.
Dermatitis with infection	3	*Staph. aureus* in 3	Good	31.3	7.3	4.2
Pemphigus	1	*Staph. aureus*	Fair*	48.0	8.0	6.0
Furunculosis or carbuncle	4	*Staph. aureus* in 2	Good	28.1	4.7	6.0
Cellulitis	5	*Staph. aureus* in 2 *Strep. hemolyt.* in 1	Good	31.2	5.8	5.3
Abscess	5	*Staph. aureus* in 5	Good (3) Fair (2)	43.3	9.0	4.8
Wound infection	7	*Staph. aureus* in 3	Good (3) Fair (3)	27.6	6.2	4.4

* Temporary.

There were 13 patients with various infections that involved the ear, nose, and throat. These lesions were roughly grouped as follows: sinusitis (postoperative), 2 cases; otitis media, 4; mastoiditis (post-

operative), 2; vestibulitis, 1; laryngitis, 1; pharyngitis with cervical adenitis, 2; and acute tonsillitis, 1 case. *Staph. aureus* was cultured from 3 of these lesions and *Strep. hæmolyticus* from 5. Although the results from treatment in general were judged to be good, we believe that it is impossible to draw any definite conclusions from a small series of cases of this type and we do not feel that a detailed analysis is of value.

TABLE 3.—MISCELLANEOUS CONDITIONS.

Condition.	Case.	Sex.	Age, yrs.	Sulfamethylthiazole.			Comment on result
				Total dose, gm.	Total no. of days.	Av. daily dose, gm.	
Chancroid	1	M	35	40	10	4	Marked healing at time drug discontinued on dismissal.
	2	M	51	24	6	4	Marked healing at time drug discontinued on dismissal.
Lymphogranuloma inguinale	3	M	46	54	10	5.4	Marked improvement in rectal condition with relief of pain present for 14 months.
Trachoma	4	M	38	35	7	5	Ten-year history. Improvement in vision and in appearance of conjunctiva.
Bilateral uveitis	5	F	36	45	9	5	Two-year history. Previous failure of various types of therapy. On dismissal left eye improved 98% and right eye 75%.
Meningitis (*Esch. coli* with brain abscess)	6	M	52	56	9	5.2	Three-month history with previous hemolytic streptococcal meningitis. Improved and negative spinal fluid culture.
Chronic ulcerative colitis	7	M	22	71	13	5.4	Improvement with decrease in number and consistency of stools to normal and absence of blood in stools.
Indeterminate fever	8	F	45	31	9	3.4	No benefit. Postmortem examination later revealed extensive thrombophlebitis.
Cholangitis; biliary cirrhosis	9	F	31	25	5	5	Previous failure of neoprontosil therapy. Striking result; patient afebrile and clinically improved in 24 hours.
Fracture dislocation, 5th cervical vertebra	10	F	18	73.5 39	12 6	6.1 6.5	Patient with partial Brown-Séquard syndrome seen 48 hours after accident. Paralysis of muscles of thoracic wall and of deglutition. Urinary retention. Unusual recovery without complication with use of drug as prophylactic.
Localized purulent bronchitis	11	M	43	47	7	6.7	Six weeks of illness with fever and cough. Bronchoscopy revealed localized purulent bronchitis. Temperature normal after 6 days of treatment.
Empyema	12	F	51	24.5	8	3	Three weeks of illness. Rib resection necessary. No benefit from the drug.
Postoperative pneumonectomy	13	M	44	80.5	11	7.3	*Strep. viridans* in chest fluid. Decline in temperature to 99° F. after 6 days of treatment.
Postoperative thoracotomy for cyst of lung	14	M	34	30	6	5	*Staph. aureus* in drainage. *Pneumoniæ* Type D in sputum. Decline in temperature to 99° F. in 4 days.

Three patients with infections of the urinary tract were treated and all improved. *Staph. aureus* was recovered from the urine of 1 patient and *Strep. fæcalis* from the urine of another.

Fourteen patients have been listed in a miscellaneous classification which includes the conditions given briefly in Table 3.

Comment. One hundred and six patients with various types of infections have been treated with sulfamethylthiazole. The diseases for which treatment was given together with the number in each group have been roughly classified as follows: pneumonia, 30 cases; septicemia, 7; subacute bacterial endocarditis, 5; pelvic infections, 5; bone infections, 4; cutaneous infections, 25; infections of the ear, nose and throat, 13; urinary infections, 3; and miscellaneous types, 14 cases.

Sulfamethylthiazole was administered orally to the majority of patients in doses similar to those employed when we have used sulfanilamide and sulfapyridine, with the exception that larger doses were frequently used for and tolerated by the severely ill patients. The sodium salt of sulfamethylthiazole was used intravenously for 3 patients and it produced significant elevations of the concentration of the drug in the blood.

Sulfamethylthiazole, when used orally, produced concentrations of the free drug in the blood similar to but somewhat lower than those resulting from the use of sulfapyridine, and a minimal amount of conjugation occurred.

We realize that it is not possible to draw conclusions which may be entirely satisfying from a small series of 106 cases. We believe, however, that the results obtained to date justify confidence that the clinical, therapeutic effect of sulfamethylthiazole substantiated experimental predictions. Infections produced by the *Staph. aureus* and the *Diplococcus pneumoniæ*, Type I, in particular seem to respond to treatment.

With the exception of the highly important and significant complication of lower motor neurone involvement in 3 cases and of cutaneous eruptions in 9, toxic effects seemed to be less than we have encountered with the use of sulfapyridine and also sulfanilamide. Significant nausea and emesis occurred infrequently. No serious disturbances resulted in the number of erythrocytes or leukocytes. No decline in the carbon dioxide-combining power of the blood was noted. No renal complications occurred save in 1 case in which acetylsulfamethylthiazole crystals formed in the renal pelves.

Summary. Sulfamethylthiazole* was used orally in 106 cases for various types of infections and the drug seemed to produce satisfactory results in a significant number. This was particularly true

* Since this study was completed and recorded, sulfamethylthiazole has been withdrawn from clinical experimental use owing to occurrence of the complication of lower motor neurone involvement.

of infections produced by the *Staph. aureus* and the *Diplococcus pneumoniæ*, Type I.

Lower motor neurone involvement giving rise to muscle weakness was the most significant toxic manifestation encountered and toxic manifestations otherwise seemed mild in comparison with those associated with sulfapyridine and sulfanilamide.

The danger of lower motor neurone involvement as a complication leads us to believe it unwise to use sulfamethylthiazole for mild infections caused by *Staph. aureus*, which we have previously felt justified in treating. However, when one is dealing with a fulminating infection such as a septicemia which carries an exceedingly high mortality rate that far outweighs the danger of toxic manifestations from drug therapy, this drug or a related preparation may still find a field of usefulness.

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THE ANTIPYRETIC ACTION OF SULFAPYRIDINE.

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Since the introduction of the sulfonamide compounds for the treatment of infections it has been suggested by some observers that these drugs might have an antipyretic action. This applies particularly to sulfapyridine. Ellis,[1] in reporting the effect of sulfapyridine in subacute bacterial endocarditis, says: "The profound fall in temperature that can be produced by large doses, such as 4–6 grams in twenty-four hours . . . . makes one wonder

whether some temperature-reducing mechanism may not be at work, other than the mere destruction of organisms." Major,[3] discussing the same disease, says: "The effect upon the temperature may not, however, be specific, since there is evidence that this drug has temperature lowering effects." Similarly, in pneumonia sulfapyridine often causes a fall in temperature in so short a time as to make it seem unlikely that the effect is entirely on the infectious process. Flippin, Schwartz and Rose,[2] comparing the effectiveness of sulfapyridine and sulfathiazole in the treatment of pneumonia, noted that a critical fall in temperature during the first 24 to 48 hours occurred more frequently in patients treated with sulfapyridine than in those treated with sulfathiazole, although they found no difference in the end-results with the two compounds.

Clinical demonstration of an antipyretic action of these drugs is difficult; usually one cannot exclude the possibility that the fall in temperature is due to an effect on the underlying infection. Certainly, the antipyretic action of sulfapyridine is not as great as that of the salicylate compounds or amidopyrine. However, the authors wish to cite the following cases in which it seems probable that sulfapyridine exerted some antipyretic action.

Case Reports. Case 1.—W. W., male, age 42, febrile illness of 6 weeks' duration. No specific complaints other than fever, weakness and malaise. Physical examination showed emaciation, a "doughy feeling" abdomen, palpable cecum, and an indefinite mass in the epigastrium. Laboratory findings: mild secondary anemia, normal white blood cell count with shift to left, urine normal, tuberculin test strongly positive. After the period shown on the chart, the patient developed Roentgen ray evidence of miliary tuberculosis of the lungs and the tuberculin test became negative. Clinical diagnosis: tuberculous peritonitis with miliary tuberculosis. At autopsy, a large mass of caseous tuberculous glands was found surrounding the celiac axis and extending up the thoracic duct for several centimeters. There was generalized miliary tuberculosis. Figure 1 shows the effect of sulfapyridine on the fever. Note that temperature level fell with each course of sulfapyridine, but was not affected by a course of sulfathiazole. Blood levels: Sulfapyridine (first course) free 4.4 mg. per 100 cc., combined 2.1 mg. per 100 cc. Sulfathiazole free 4.9 mg. per 100 cc., combined 0.9 mg. per 100 cc. Sulfapyridine (second course) free 6.9 mg. per 100 cc., combined 2.1 mg. per 100 cc.

Case 2.—C. M., male, aged 63, admitted after an illness of 1 week. Physical examination and Roentgen ray indicated fluid in right pleural cavity. As shown in Figure 1, purulent fluid containing *Staph. aureus* was obtained by thoracentesis on two occasions and continued to thicken and increase in amount during the period of observation. After 8 days thoracotomy was done. The chart shows the effect of sulfathiazole, sulfapyridine and sulfamethylthiazole on the temperature level before operation. It is unlikely that any of these drugs had much effect in retarding the intrapleural infection, yet while sulfapyridine was being administered the temperature level was depressed. Blood levels: Sulfathiazole free 3.7 mg. per 100 cc. Sulfapyridine free 7.9 mg. per 100 cc. Sulfamethylthiazole free 5 mg. per 100 cc.

Case 3.—E. W., male, age 38, admitted for study of an illness of 5 years' duration, characterized by the regular recurrence of fever every fifth day.

No evidence of infection was found after extensive studies. Cause of fever undetermined. On the chance that some infection might be present which would be amenable to treatment with the sulfonamide drugs, the patient was given sulfanilamide and later sulfapyridine. The depression of the expected temperature level by sulfapyridine is evident from the chart in Figure 1. That this effect was an antipyretic one is suggested by the fact that amidopyrine administered at a later date completely abolished the usual paroxysm of fever.

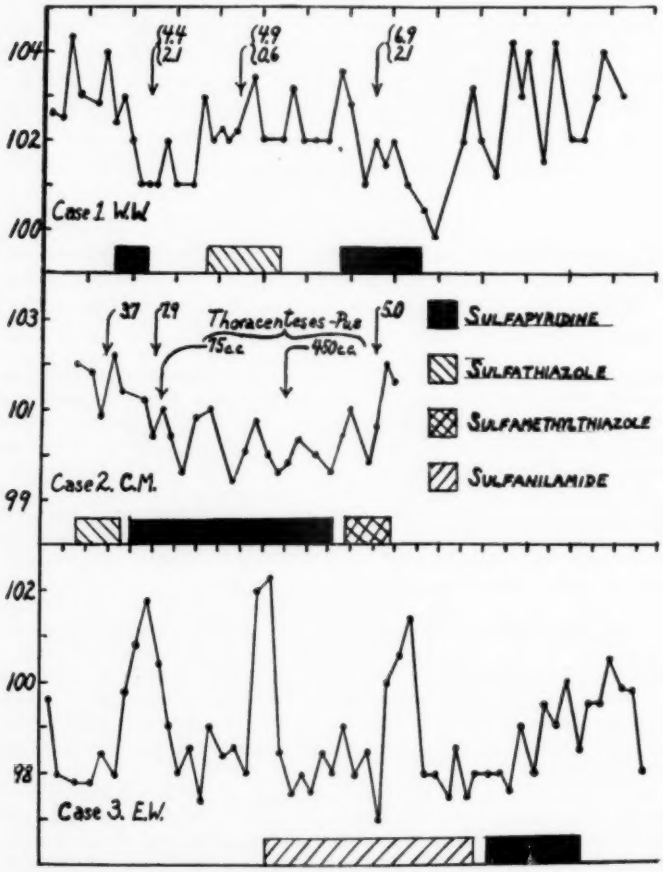
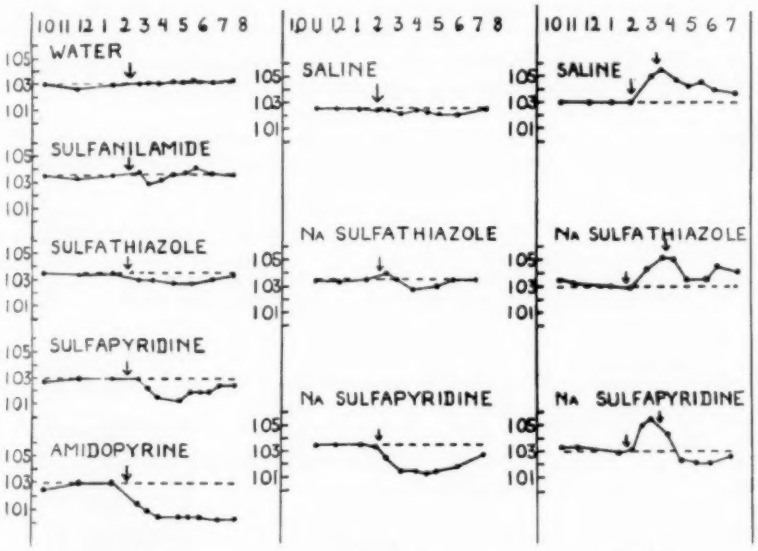


FIG. 1.—Effect of administration of sulfonamide compounds on temperature of patients in whom a direct chemotherapeutic effect may be reasonably well excluded. Numerals with arrows indicate blood concentration of the drugs. Where one figure is given it represents the level of free drug. Where two are given, the upper figure represents the concentration of free and the lower the concentration of combined drug.

Experimental. Experiments carried out in rabbits to test the effect of the sulfonamide compounds on the body temperature are reported herewith.

Materials and Methods. Adult female rabbits were used as experimental animals. White rabbits were used exclusively in later experiments, as it was found that results were more uniform with them. The drugs were administered after a preliminary period of several hours during which the normal rectal temperature for each rabbit was ascertained. For oral administration the drugs were suspended in 20 cc. water, warmed to body temperature and given by stomach tube. For intravenous injection the sodium salts of sulfapyridine and sulfathiazole were dissolved in warm distilled water and injected into the ear vein. In all experiments control animals were given equal amounts of water or saline by the same route of administration. Standard commercial typhoid vaccine was injected intravenously in some experiments in order to produce fever.



Graph 1. *Graph 2.* *Graph 3.*

FIG. 2.—*Graph 1:* Effect of oral administration on normal temperatures of rabbits. One gram of test substance in 20 cc. of water given by stomach tube at arrow. *Graph 2:* Effect of intravenous administration on normal temperatures of rabbits. Five-tenths gram of test substance in 10 cc. distilled water injected at arrow. *Graph 3:* Effect of intravenous administration on temperatures of rabbits with pyrexia induced by typhoid vaccine. Five-tenths cubic centimeter of diluted typhoid vaccine injected at first arrow, 0.5 gm. of test substance in 10 cc. distilled water injected at second arrow.

Results. 1. *Effect of Oral Administration of Sulfanilamide, Sulfapyridine and Sulfathiazole on the Normal Temperature* (Fig. 2, Graph 1). Sulfanilamide and sulfathiazole had only a slight temperature-lowering action, but sulfapyridine was considerably more effective. Amidopyrine had a still greater effect. It should be noted that all drugs were given in equal amounts (1 gm.) in these experiments, whereas in clinical usage the dose of the sulfonamide compounds is usually many times as great as the dose of amido-

pyrine. Although the doses used were proportionately greater than those used in humans, the blood levels achieved were comparable, *e. g.*, 15 mg. per 100 cc. for sulfanilamide and 5 mg. per 100 cc. for sulfapyridine 3 hours after oral administration of 1 gm.

2. *Effect of Intravenous Administration of Sulfapyridine and Sulfathiazole on Normal Temperature.* The sodium salts of sulfapyridine and sulfathiazole dissolved in water were injected intravenously in doses of 0.1, 0.5 and 1 gm. With the smallest dose there was no appreciable effect on normal temperature. However, with either of the larger doses animals which received sulfapyridine showed a marked fall in temperature, while those receiving sulfathiazole showed little or no change in temperature. The alkalinity of these two salts is the same. Typical results are illustrated in Figure 2, Graph 2. The blood levels attained were somewhat higher than those usually encountered clinically, as shown in Table 1.

TABLE 1.—BLOOD LEVELS AND TEMPERATURE OF RABBITS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF SODIUM SULFAPYRIDINE AND SODIUM SULFATHIAZOLE.

			Blood concentration (mg. per 100 cc.).						
			15 min. after injection.		3 hrs. after injection.		Temperature* (° F.) at		
Rabbit.	Drugs.	Dose, gm.	Free.	Combined.	Free.	Combined.	Start.	1½ hrs.	3 hrs.
1	Sodium sulfathiazole	0.5	17.1	3.1	2.1	0.8	103.0	102.7	102.8
2	Sodium sulfathiazole	0.5	25.5	2.2	6.3	0.5	103.0	103.2	102.9
3	Sodium sulfapyridine	0.5	19.2	8.6	1.9	9.3	102.6	101.5	102.5
4	Sodium sulfapyridine	0.5	11.6	2.8	1.2	6.4	103.0	102.2	102.0

* The fall in temperature in this particular experiment was less striking than usual, probably because of the warm, humid day.

3. *Effect of Sulfonamide Compounds on the Fever Produced by Intravenous Administration of Typhoid Vaccine.* By the intravenous administration of typhoid vaccine, sharp temperature rises can be produced in rabbits; the rise usually begins about 30 minutes after injection and reaches its peak in an hour. When sulfanilamide, sulfathiazole and sulfapyridine were given orally before the vaccine injection the temperature responses of the animals were little different from those in the controls, except that there seemed to be a more rapid return to normal temperature in the rabbits which had received sulfapyridine. Similarly, when sodium sulfapyridine and sodium sulfathiazole were given intravenously before or at the same time as the vaccine there was no reduction in the height of fever attained by the treated animals, as compared with the controls, although animals which received sulfapyridine showed a more rapid return to normal temperature than the others. On the basis of these results a series of experiments were carried out in which sodium sulfapyridine and sodium sulfathiazole were given

intravenously when the peak of fever had been reached after the injection of typhoid vaccine. A typical experiment is illustrated in Figure 2, Graph 3. Animals receiving sodium sulfapyridine showed a rapid drop in temperature to the normal level or below, while those receiving sodium sulfathiazole underwent little or no drop in temperature, and did not reach normal any sooner than the controls.

4. *Effect of Acetyl Derivatives of Sulfonamide Compounds on Normal Temperature.* Since sulfapyridine and sulfathiazole differ in the extent to which they are acetylated in the blood of rabbits and humans, this might explain the difference between them in antipyretic action. Accordingly, the acetyl derivatives were tested for their effect on the normal temperatures of rabbits. Several experiments were performed using the oral route of administration and doses of 1 gm. It was possible to obtain satisfactory blood levels of both acetyl sulfanilamide and acetyl sulfapyridine by this method, but not of acetyl sulfathiazole, which is very insoluble. In these experiments neither acetyl sulfanilamide nor acetyl sulfapyridine affected the temperature significantly (blood concentrations were 5 to 10 mg. per 100 cc. of combined drug and less than 1 mg. per 100 cc. of free drug).

TABLE 2.—BLOOD LEVELS AND TEMPERATURES OF RABBITS FOLLOWING THE INTRAVENOUS ADMINISTRATION OF SODIUM SALTS OF THE ACETYL DERIVATIVES OF THE SULFONAMIDE DRUGS.

Rabbit No.	Drug.	Dose, gm.	Blood concentration, mg. per 100 cc. Time of sample.	Free.	Combined.	Temperature. Start.	1½ hrs.	2½ hrs.	3½ hrs.
Experiment 1 at Room Temperature of 80° F.									
17	Sodium sulfapyridine	0.5	..	..	..	102.8	102.2	102.3	
4X	Sodium acetyl	0.5	1½ hrs.	0.7	14.8	102.4	101.8	..	101.8
9	sulfapyridine	0.5	"	1.7	19.1	103.6	103.3	..	104.1
4	Sodium acetyl sulfathiazole	0.5	"	1.8	29.8	103.0	102.0	..	101.8
16	Sodium acetyl sulfanilamide	0.5	"	0.8	10.2	102.4	102.4	..	103.3
Experiment 2 at Cold Room Temperature of 45° F.									
4	Sodium sulfapyridine	0.5	2½ hrs.	21.2	22.4	103.0	100.6	101.0	101.5
17	Sodium acetyl	0.5	"	1.0	15.2	103.7	101.3	101.0	102.0
16	sulfapyridine	0.4	"	0.9	5.4	103.0	101.8	102.6	102.8
4X	Sodium acetyl	0.5	"	1.8	5.9	103.5	103.8	103.7	103.7
9	sulfathiazole	0.5	"	0.5	5.3	103.0	102.3	101.9	103.2
5	Sodium acetyl sulfanilamide	0.4	"	0.5	9.5	103.9	103.9	103.8	103.6

In order to get more satisfactory blood concentrations the drugs were dissolved in dilute sodium hydroxide, the excess alkali was neutralized by adding hydrochloric acid until a precipitate just began to appear, and these solutions were injected intravenously. Table 2 gives the results obtained in two experiments performed at different environmental temperatures. It is obvious that sodium acetyl sulfanilamide produced no change in the temperature, but it is more difficult to evaluate the effect of sodium acetyl sulfapyridine and sodium acetyl sulfathiazole. The latter drug lowered the temperatures of 2 of 3 rabbits. In Experiment 1 this effect per-

sisted, and in this rabbit the blood concentration was excessively high. Similarly, with sodium acetyl sulfapyridine, there was a lowering of the temperature of 3 of the 4 rabbits tested, but the effect only persisted in 2, and in these rabbits (No. 4X in Experiment 1 and No. 17 in Experiment 2) the blood levels were also high. If the temperature-lowering action of sulfapyridine is due to the formation of acetylated sulfapyridine in the body fluids, the intravenous injection of large amounts of sodium acetyl sulfapyridine should produce a much more extreme change in body temperature. Since this did not occur, we must conclude that acetyl sulfapyridine has some temperature lowering activity, but less than that of the free compound. The same seems to be true of sulfathiazole.

Mechanism of Action. Rises in body temperature may be caused by increased heat production, decreased heat loss, or both. Observation of the color and warmth of the rabbits' ears during these experiments suggested that some of the drugs acted to produce an increased loss of heat through the skin. Whenever the temperature was falling, as a result of the administration of amidopyrine, sodium salicylate, or sulfapyridine, the ears of the rabbits were warmer than those of rabbits whose temperatures were not falling. A few experiments were done to test this hypothesis. When rabbits were placed in an incubator room (temperature of 98° F. and high humidity) their temperatures rose to about 105° F., their ears became hot, and they panted and appeared prostrated. *Neither sulfapyridine nor amidopyrine had any effect in lowering the temperature under these circumstances.* When rabbits were placed in a cold room (temperature 45° to 50° F.) their body temperatures ranged between 102° and 103° F., their ears became cold, and the skin vessels were constricted. After the administration of sulfapyridine or amidopyrine there was a rapid fall in temperature, and the ears of the treated rabbits became warm.

Discussion. The measurement of changes in heat production was not feasible, hence it is impossible to go further than to state that the antipyretic action of sulfapyridine in rabbits is at least partially mediated through increased dissipation of heat from the skin. When that mechanism is thwarted, as in the incubator experiments, no fall in temperature occurs. Conversely, when the differential between body and air temperature is marked, as in the cold room experiments, a greater drop in temperature occurs.

These experiments indicate that sulfapyridine has a much more marked effect on the body temperature than sulfanilamide or sulfathiazole. This may be a point of some importance in the clinical evaluation of the effectiveness of these drugs, as in the comparison of sulfathiazole and sulfapyridine in the treatment of pneumonia.

Summary. 1. Clinical examples are presented in which it appeared that the fall in temperature following administration of sulfapyridine was due to an antipyretic action rather than to any effect on the infectious process.

2. In normal rabbits sulfapyridine caused significant lowering of the body temperature, while sulfanilamide and sulfathiazole caused only slight changes. Sodium sulfapyridine administered intravenously caused a prompt fall in body temperature, whereas, sodium sulfathiazole caused a slight drop.

3. Sodium sulfapyridine given intravenously at the height of fever induced by typhoid vaccine produced a rapid fall to normal or subnormal temperature. Sodium sulfathiazole exerted a slight antipyretic action under these circumstances.

4. In normal rabbits acetyl sulfanilamide did not affect body temperature when given orally or intravenously as its sodium salt. Acetyl sulfapyridine and acetyl sulfathiazole did not affect the temperature when administered orally, but when given intravenously as their sodium salts produced a persistent drop in body temperature in certain rabbits with high blood concentrations. Sodium acetyl sulfapyridine was more effective than sodium acetyl sulfathiazole, but both drugs were less effective than the free compounds.

5. As far as could be ascertained, most of the antipyretic action of sulfapyridine was due to increased dissipation of heat from the skin.

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The sulfanilamide used in this study was supplied by the Research Department of the Winthrop Chemical Company; the sulfamethylthiazole by the Maltbie Chemical Company; the sulfathiazole by the Squibb Institute for Medical Research; and the acetyl derivatives of these drugs by the Calco Chemical Company and the Lederle Laboratories.

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INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE.

XV. The Absorption and Expulsion of Glucose from the Stomach.*

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The work of several groups of investigators (London and Polowzowa;[7] Maddock, Trimble and Carey;[9] Macleod, Magee and

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Purves[8]) has given rise to the opinion that glucose is not absorbed from the stomach. A review of the literature, however, reveals that the majority of evidence (v. Anrep;[3] Tappeiner;[17] Brandl;[4] Holtz and Schreiber;[6] v. Mering;[11] Morrison, Shay, Ravdin and Cahoon,[12] and others) is actually opposed to this viewpoint. Especially certain experimental work on man (Strauss;[16a] Freund and Steinhardt;[5] Shay, Gershon-Cohen and Fels[14]) supports the idea that glucose can leave the stomach by routes other than its two orifices. The present investigation was designed to examine this problem more closely, using the normal human as the experimental subject. The study is divided into three parts: (*a*) the disappearance of glucose from the stomach with the pylorus functioning; (*b*) its disappearance from the stomach and duodenum as a unit; (*c*) its disappearance from the stomach with the pylorus mechanically closed.

Method. (*a*) *Disappearance of Glucose From the Stomach With the Pylorus Functioning.* To normal human subjects, fasting and after the introduction of a gastric tube, test glucose solutions of widely differing concentration were given by mouth. After a measured time the stomach contents were aspirated; the stomach was then thoroughly washed over an additional period of 5 minutes, and all the recovered material was analyzed for its glucose content. The amount lost was calculated per unit of time and usually expressed as loss in grams per hour. In some subjects a second tube was passed through the pylorus to remain throughout the experiment. As the data in the latter cases were similar to those in the former, they have been included in the results without differentiation.

Results. Chart 1 shows the grams leaving the stomach per hour plotted against the product of the volume in cc. and the concentration in gm./100 cc. introduced. This product is used in preference to grams introduced only because it conveys the idea that the grams leaving are proportional to the volume of the solution introduced as well as the osmotic gradient due to concentration. There is a suggested relationship. Such a definite scattering of the points, however, implies that the governing factors regulate the process rather loosely. These factors are discussed in the following sections.

It is more important to note that with higher volumes and concentrations it is not uncommon for the stomach to lose 60 to 120 gm. of glucose per hour. On one occasion 190 gm. were lost. These quantities are significant relative to the data presented in the next section.

Method. (*b*) *Disappearance From the Gastro-duodenal Unit.* Normal subjects were intubated with a tube having two lumens and a terminal balloon on one of them. An attempt was made to keep the balloon in an area just distal to the duodenal-jejunal juncture. To this end the experiment was performed with the subject on a fluoroscopic table and observations as to its location were made at 5-minute intervals. An opening in the second lumen just proximal to the balloon was used for continuous aspiration of the contents as they left the duodenum. In some instances

a second balloon slightly below the first with facilities for aspiration between them was used as a detector for leakage past the first balloon.

Glucose solutions were given by mouth. In some experiments, at the end of a fixed period, usually about 30 minutes, the stomach was emptied. Immediate repeated washes of the stomach and duodenum with water removed any residual glucose within a few minutes. In other experiments absorption was allowed to continue until the duodenal contents were practically sugar-free. When the stomach was washed, the amount of glucose leaving the stomach was calculated in grams per hour.

Subtracting the glucose return of the stomach and duodenum from the amount ingested gave the absorption by the total unit.

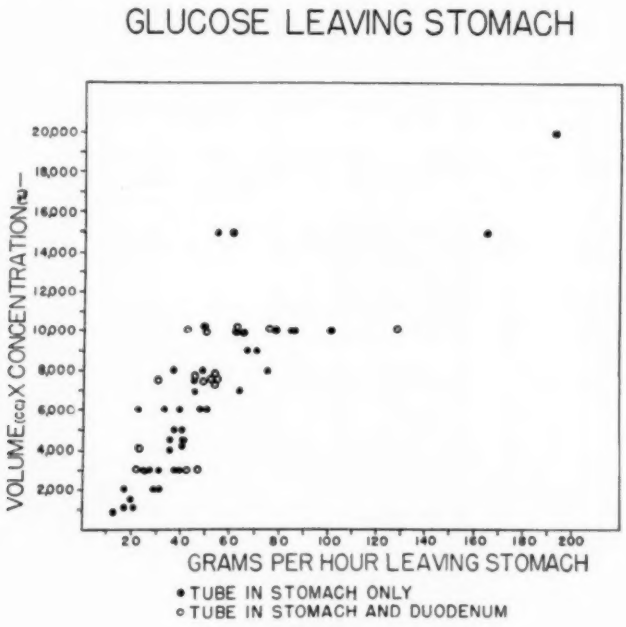

CHART 1.

The material appearing in the upper jejunum was collected in each experiment as a series of specimens, each of which was analyzed separately. The time intervals for each specimen were variable because they were determined by the volume of flow. The total volume of fluid and amount of glucose entering the jejunum were determined.

Results. The results of 25 experiments on 9 subjects are shown in Table 1.

Discussion. There was a marked inconstancy in the amount of glucose that entered the jejunum from the duodenum. This was noted even in the same individual on different occasions under similar experimental conditions. In most instances it represented only a small fraction of the amount ingested or the amount absorbed

above the duodenal-jejunal juncture. Presumably, therefore, most of the glucose ingested is absorbed above the jejunum while the remainder of the small intestine is available to function when there is excess glucose ingestion, increased motility, decreased absorption, increased hydration, and so on.

TABLE 1.—GASTRO-DUODENAL ABSORPTION OF GLUCOSE.

Subject No.	Case No.	Stomach.				Jejunum.		Gastro-duodenal unit.		
		In		Leaving		Enter		Absorbed	Duration in duod.	Absorbed
		Gm.	%	Min.	Gm./hr.	Cc.	Gm.	Gm.	Min.	Gm./hr.
I	207	24	50	..	..	90	1.3	21.5	193	6.3
III	220	25	50	..	..	182	3.5	21.5	300	4.3
I	211	25	50	..	..	42	1.8	23.7	195	4.4
II	219	25	50	..	..	160	2.7	22.3	180?	7.4
II	208	25	5	..	..	42	0.8	23.0	195	6.3
III	215	25	5	..	..	387	6.9	18.0	213	5.1
IV	163	27	5.4	32	36	186	6.8	12.3	38	19.4
VII	148A	30	15	34	42	166	5.8	17.9	100	10.8
IX	149A	30	15	31	21	106	1.4	9.5	84	6.8
VIII	147A	30	15	32	46	67	1.3	23.4	73	19.2
IX	149B	40	20	33	21	82	0.3	11.2	63	10.7
IV	145	50	25	..	..	74	2.6	47.4	147	19.3
VII	146	50	25	..	..	621	19.2	30.8	163	11.4
IV	151	75	25	50	48	0	0.0	40.7	60	40.7
V	159	75	25	33	51	157	7.7	20.3	40	30.4
III	150	75	25	40	53	40	1.2	34.2	73	28.1
VI	152	75	25	30	30	71	2.6	12.5	30	25.0
IV	161	75	25	32	51	123	7.9	18.4	42	26.2
V	162	75	25	33	45	204	13.0	11.9	42	17.0
IV	158	75	25	31	52	6	0.3	26.6	37	43.2
V	157	100	20	31	42	38	1.1	19.0	37	30.8
IV	156	100	33	32	62	101	7.3	25.6	39	39.4
V	155	100	33	33	50	195	9.6	16.9	40	25.4
IV	154	100	33	172	32	57	2.2	87.9	180	29.2
VI	160	150	50	32	55	134	14.4	12.9	37	20.8

There was less variation in the amount of glucose leaving the stomach per hour. If, as indicated in the following section, glucose leaves through the stomach wall only in the first short period of contact then this calculation of grams per hour leaving is influenced by the time interval that the glucose is allowed to remain in the stomach.

In general, the amount absorbed by the gastro-duodenal unit varies directly with the amount and concentration of the glucose.

Inspection of the table, furthermore, shows that the absorption for the gastro-duodenal unit is often greater than that anticipated by duodenal absorption[2] alone. Also the amount of glucose which leaves the stomach per hour is often greater than the sum of that usually absorbed from the duodenum[2] and that discharged into the

jejunum from the duodenum. From these observations we may infer that some glucose leaves through the stomach wall.

Method. (*c*) *Disappearance of Glucose From the Stomach With the Pylorus Occluded.* Only professional subjects whose normal health had been assured by physical examination and by the determination of the presence of free acid in the gastric secretion were used. A set of tubes and balloons, the efficiency of which in occluding the pylorus has previously been reported by one of us (Warren[18]), was manipulated into position under the fluoroscope. In some of the experiments a 3-lumened tube was used instead of the double-lumened tube with a thin tube placed parallel with it. The experiments were carried out with the subject either in the supine position or tilted very slightly toward the left side. Through the tube communicating with the stomach cavity solutions of glucose of varying concentration but, with one exception, of constant volume were introduced at body temperature. These were again withdrawn either immediately or at the end of measured periods approximating 30 minutes. At the end of the withdrawal the stomach was washed with tap water in 200 cc. portions while the subject rotated her body until the returning wash was glucose-free as shown by Benedict's qualitative test. The wash usually took about 15 minutes and involved the use of 600 to 800 cc. of water. Throughout the absorption period constant suction was applied in the duodenum beyond the balloons and the resulting accumulated duodenal specimens were withdrawn and tested with Benedict's qualitative solution. In a few of the experiments 10 cc. of 0.5% vital red solution were mixed with the test solution before injection, thus permitting a further check on the escape of gastric contents into the duodenum. Fluoroscopic observations were repeated during and at the end of the test periods. Any experiments in which the duodenal specimens contained glucose or in which the balloons did not stay satisfactorily in place were discarded.

Glucose analyses were carried out by the method previously described.[1] The experimental period was taken arbitrarily as extending from the beginning of the injection of the solution to the onset of the wash. We feel that the contents remaining after the initial aspiration are so diluted by the washes that concentrations well below the isotonic level must be immediately reached as soon as the wash water is introduced. Since other experiments have shown that glucose in such concentrations is not absorbed, it seemed justifiable so to limit the experimental period.

In 6 of the experiments the time period lay between 16 and 37 minutes. One additional experiment, designated by the single asterisk, is added to this group, but is to be mentioned separately because it was not quite so carefully controlled. In 5 experiments the glucose solution was aspirated as quickly as possible after introduction. These are tabulated for comparison alongside the experiments with the longer periods in which comparable concentrations of glucose were used.

Results. The results of 12 experiments are listed in Table 2. It is to be noted that the amounts of glucose lost from the concentrations of 11.2% and below were less than 1.7 gm. out of total amounts injected varying between 5.5 and 27 gm. The amounts lost in the other experiments were roughly the same, with the exception of the 40% concentrations, whether the glucose was allowed to remain in the stomach one-half hour or whether it was aspirated

immediately. In other words, the absorption that occurred must have taken place very soon after the injection.

It is apparent from examining the data that the amounts of glucose lost, regardless of the concentration or experimental period, correspond to volumes of from 11 to 30 cc. of the original solution. A control experiment to test whether this might be due to mechanical loss of solution in manipulation of the tubes consisted of injecting and aspirating a 41% glucose solution through the same tube used in the experiments into a rubber balloon and washing out afterwards. It was found that in this procedure only 0.69 gm. was lost, revealing an almost negligible error due to mechanical loss.

TABLE 2.—GLUCOSE ABSORPTION FROM THE STOMACH.

Subject.	Glucose injected. Cc.	%.	Gm.	Glucose recovered, gm.	Duodenal glucose, gm.	Glucose lost, gm.	Experimental period,† min.
C. B.	250	2.46	6.15	5.40	0	0.75	33
C. B.	145	5.0	7.25	6.36	0	0.89	32
F. S.	250	5.0	12.50	11.33	0	1.17	5½
M. H.	250	5.0	12.50	11.95	0	0.55	34
M. P.	245	5.0	12.25	10.61	0	1.64	4
C. B.	254	11.2	28.58	27.08	0	1.50	32
M. P.	250	20.0	50.00	45.37	0	4.63	16
C. B.	250	19.1	47.80	42.60	0	5.20	4½
C. B.*	250	40.0	100.00	86.68	0	13.32	37
C. B.	250	39.3	98.30	91.80	0	6.50	5½
M. P.	249	60.0	149.40	129.65	0	19.75	35½
M. P.	250	60.3	150.80	133.10	0	17.70	7½

* In this experiment barium mixed with the glucose instead of aspiration of duodenal contents was used to check the efficiency of the block.

† Measured from onset of injection to onset of wash.

Discussion. The mechanism of absorption in the stomach has been accepted, by most of those who believe it occurs, as a physical process of diffusion, in contradistinction to the special absorptive process present in the small intestine which enables the mucosa to extract sugar from a hypotonic solution. While Roth and Strauss[13] and Strauss[16b] have defended this physical explanation, others have felt that, were it so, far more sugar would pass through the mucosa than direct observation has indicated.

It is important to note, however, that the concentration of strong glucose a short time after it reaches the stomach varies depending on the location from which the sample is obtained. The stomach is often described as a good mixing organ but it is only because this is not the case that the ingestion of a concentrated solution can be followed so promptly by the evacuation of a dilute solution. As a matter of fact, a definite concentration gradient, highest at the

center of the gastric mass and lowest at its periphery, is rapidly established, a point which is not apparent if a sample of the total mixed gastric contents is taken as indicative of the true conditions within the stomach. This fact is illustrated by the results of an experiment upon a dog. From the stomach, isolated *in situ* and filled with 50% glucose, 2 simultaneous specimens were aspirated 10 minutes later. The concentration of the one from the center of the contents was 40.2% while that from near the periphery was 18.3%. The suggestion is obvious that the concentration of the most peripheral layer actually adjacent to the epithelial cells would have been even lower.

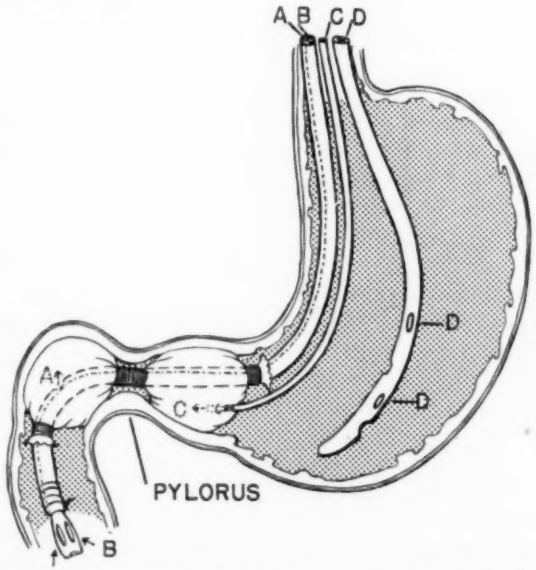

FIG. 1.—*Technique of obstructing the pylorus.* *A*, Balloon in duodenal cap and tube lumen through which air is injected into the balloon; *B*, aspirating tip in duodenum and lumen through which duodenal content is constantly aspirated throughout the experiment; *C*, balloon proximal to the pylorus and fine tube through which air is injected to distend it; *D*, large lumened Levine tube for filling and emptying the stomach.

It is also obvious that, if the concentrated glucose contents of the stomach were only separated from the blood and tissue fluids by a membrane permeable to both glucose and water, diffusion would continue as long as the stomach contents were hypertonic. Some other explanation for the cessation of the removal of glucose through the stomach wall seems necessary. We can only conjecture that it may be concerned with the secretion of mucus. Magee[10] and others have shown that there is a marked secretion of mucus in response to the apparently irritating action of strong glucose.

This might form some protective covering over the walls of the stomach through which glucose would diffuse slowly as through a gel.

We are inclined therefore to the view that the stomach is "not adapted" to glucose absorption. When, however, unphysiologic amounts of strong diffusible glucose are ingested its hypertonicity causes a certain amount to pass through or into the stomach wall until in a short time it is inhibited by some mechanism.

General Discussion. It is important to differentiate what seems to be the usual mechanism of action of the stomach and duodenum in response to the ingestion of glucose from certain striking variations which may occur in different individuals, or in the same individual under comparable experimental conditions on different occasions. The factors responsible for these variations are obscure. Under the conditions of experimentation reported in Section *b*, glucose did not leave the stomach at a greater rate than 62 gm./hr., while with a greater number of cases, as shown in Chart 1, this figure was often exceeded. That the subjects used for the experiments in Section *b* were selected from coöperative individuals accustomed to intubation may explain the difference.

In the light of these observations and of those presented previously in the series, we may generalize concerning the mechanism involved in the disposal of concentrated glucose solutions ingested into the alimentary canal. As a concentrated solution hits the wall of the stomach a certain amount is removed in the first short period of contact. Equally quickly there occurs a movement of fluid from the mucosa into the gastric cavity, but this does not occur as rapidly as one would anticipate on the basis of simple diffusion through a membrane, and a high concentration of the contents as a whole is well maintained. Only gradually does this decrease as the balance between the movement of fluid into the stomach and of fluid and glucose out of the stomach shifts in favor of increasing dilution. As the gastric contents slowly circulate in response to the mixing action of peristalsis, the peripheral layer moving caudad and the central column orad, that portion entering the antrum is exposed to a rapid change in the conditions that govern this balance. The ratio of mucosal surface to contained solution increases rapidly, until as the glucose reaches the pylorus at the apex of the conical antrum, it is that portion which has been longest in contact with the gastric mucosa that enters the duodenal cap and that which has had least opportunity for dilution that is returned toward the fundus. Whether or not this mechanism alone is accountable, the fact remains that the stomach begins within a few minutes to put out small quantities of its contents at a concentration never observed by us to exceed 15%. In this sense the stomach is seen to be a highly efficient diluting organ, acting as an effective barrier against the entry of highly concentrated solutions into the duodenum. From

the standpoint of the gastric residue, however, it is striking to observe how slowly the concentration of the total mixed gastric contents falls, considering the osmotic gradient existing between it and the body fluids.

When the relatively small volume of glucose at a concentration of 15% or less enters the duodenum, it is almost immediately diluted still further. This is undoubtedly due to a large extent to the relatively large surface area to which it is exposed in respect to its volume. Because of this dilution and the absorption of glucose, if any sugar escapes into the jejunum it is almost never above 6% and its concentration is approaching isotonicity with the body fluids.

Glucose is rapidly absorbed by the duodenum and in many instances its capacity to absorb is sufficient to take care of all the glucose coming from the stomach so that no glucose passes into the jejunum. Previous experiments have shown that if it does pass into the lower intestine it can also be absorbed very readily there. It has been mentioned previously that nature did not intend to compel the gastro-intestinal tract to deal with such concentrated solutions with a high osmotic pressure, but as is here shown, there is a large factor of safety sufficient to handle such solutions with a maximum of safety to the human organism.

Conclusions. When concentrated glucose solutions are ingested, a certain amount leaves through the stomach wall during the first short period of contact. Indirect evidence is supported by experiments in which the pylorus is mechanically closed.

The rate at which glucose leaves the stomach is usually influenced by the volume and concentration of the solution ingested.

There is a marked variation in the response of the stomach and duodenum to the ingestion of concentrated glucose in the same and in different individuals.

The stomach and duodenum may often complete the absorption of glucose without the aid of the remainder of the small intestine.

A summary is given which presents the mechanisms involved in the handling of glucose solutions by the gastro-intestinal tract. It is a concluding résumé of this and other preceding papers of this series.

NOTE. The recent publication by Shay, Gershon-Cohen, Fels and Munro[15] of the results of experiments directed at the same problems that have concerned us but leading to somewhat different conclusions demand special comment. Any technique for the quantitative study of absorption must provide a method, 1, of recovering completely the unabsorbed fraction of the test material, 2, of starting and stopping the absorption period with maximum abruptness, and 3, of retaining the test solution in contact with the mucosa of the desired area for a given period. The pyloro-duodenal region

is unquestionably the most difficult region of the digestive tract for which to devise such a procedure because of the muscular activity that it exhibits. Though it is to a comparison of these technical points that one must first turn in attempting to weigh the significance of divergent results, not every difference in the conclusions reached is on this basis. Conflicting points of view have at times led to different interpretations being placed on the same facts.

In these experiments the efficiency of balloons in blocking the caudad flow of intestinal contents must be adequately controlled.

If absorption is to be expressed in grams/unit time the duration of the period must be clean cut. It is always easy to start an experiment quickly, but we are inclined to feel that the ideal technique is that which allows the most rapid washing out of the gut at the end of the absorption period, provided that the completeness of the recovery is not endangered. This hinges in part on the caliber of the tube lumens and forced us to the use of devices composed of fine tubes for air and large ones for fluid. Without this, our washes took far too long to perform.

The efforts of the gut to dislodge test solutions are exasperatingly effective. We were not able to prevent regurgitation of fluid from duodenum to stomach and so had to devise a technique that assumed its occurrence and provided for its removal. Neither were we able to prevent the advance of balloons from the duodenum to the jejunum though it was only by frequent fluoroscopy that we appreciated how constantly this took place.

Such differences in method we believe account for the differences in the observed rates of absorption. Differences in point of view only, however, are exemplified by such statements as that the stomach is not a good diluting organ. We would agree that the material retained in the stomach is diluted slowly but we feel that the function of the stomach in this regard is to put out a fluid of low concentration and that this it accomplishes with remarkable rapidity.

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THE SABIN AGGLUTINATION TEST AND THE POLYSACCHARIDE SKIN TEST (FRANCIS) AS INDICES OF RECOVERY IN PNEUMONIA.

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Sulfapyridine so frequently causes unpleasant reactions, such as nausea and vomiting, that physicians who prescribe it in the treatment of pneumonia are often anxious to discontinue its administration at the earliest moment compatible with uncomplicated recovery. For that reason, a simple test for determining when it is safe to discontinue sulfapyridine is of importance in the management of pneumonia.

In a previous paper,[1] the authors reported the results of their studies on the development of immunity in 50 patients with pneumococcus pneumonia treated with sulfapyridine. We pointed out then that active immunity rarely develops before the eighth day of the disease, and that discontinuing sulfapyridine before that may be unwise. The present report extends that work to include 157 patients, in 151 of whom agglutinin tests (Sabin[3]) were done, and in 107 of whom skin tests with pneumococcus capsular polysaccharide (Francis[2]) were performed. Ninety-one patients received both tests. In this study we have again determined with what regularity and to what degree patients develop agglutinin to the type of pneumococcus causing their pneumonia, and what relationship this bears to the extent of the infection, the course of the illness, and the general condition of the patient. Also, we have compared the Sabin test and the Francis test as indices of immunity.

Table 1 classifies all patients who received either the Sabin or the Francis test, according to the kind of test, and to the kind of treatment. Our remarks are limited to those patients who were treated with sulfapyridine alone.

The Agglutinin Test was performed as follows: A small amount of blood, collected from the patient's ear or finger in a capillary tube, was allowed to clot. The contents of the tube were expelled to a glass slide, using a small rubber bulb such as accompanies a smallpox vaccination

outfit. The clot was lifted off with a hot wire loop, leaving the clear serum. A loopful of formolized suspension of the homologous pneumococcus* was mixed thoroughly with the serum, allowed to dry in air, fixed with heat, laked with Ruge's solution, stained with carbol fuchsin and examined under oil-immersion magnification. The degree of agglutination was classified as 0 to 4+ (see Fig. 1).

TABLE 1.—ANALYSIS OF CASE MATERIAL.

Treatment.	No. cases.	Francis.	Sabin.	Both.
None	2	2	0	0
Sulfapyridine	157	107	151	91
Serum	33	21	21	19
Total	192	130	172	110

The agglutinin test was done on 151 patients, 7 of whom died. Of the remaining 144, all but 11, who were followed to the fourteenth day of illness, developed a 3 to 4+ agglutinin test. The average time at which a strong agglutinin test was first obtained was the tenth day of illness. The earliest time such a test was obtained was the third day of the disease, and the latest was the twenty-first day. These 144 patients were divided into two categories, according to the following criteria: 76 patients who had either bacteremia, involvement of more than one lobe, a septic complication or an associated disease, were called complicated; the remaining 68 were called uncomplicated.

Table 2 shows that complicating factors cause a delay in the appearance of maximum agglutinin (from an average of 8.5 days in the uncomplicated to 12.4 in the complicated cases). This table also indicates that more prolonged treatment is required in the complicated group. The average maximum agglutinin observed in each group was the same—slightly more than 3+.

TABLE 2.—RELATION OF COMPLICATIONS TO AGGLUTININ APPEARANCE.

	No. of cases.	Average maximum agglutination.	Average day maximum agglutination first found.	Average duration treatment.
Uncomplicated cases	68	3+	8.5	4.9
Complicated cases	76	3+	12.4	7.4
Totals and averages	144	3+	10.6	6.0

The Francis Test. As performed throughout this study, the Francis test consisted of an intracutaneous injection of 0.1 cc. of a 1:1000 dilution of type-specific capsular polysaccharide.† On the opposite arm was injected a control of 0.1 cc. of physiologic solution of sodium chloride. Readings were made in 10 and 20 minutes. To be positive, there had to be a wheal as well as erythema at the site of injection.

The Francis Test as an Index of Active Immunity—Its Reliability—A Comparison With the Agglutinin Test. This test was performed

* Suspensions of nearly all types of pneumococci were supplied by the Lederle Laboratories, Inc.

† Obtained through the Lederle Laboratories for Types 1, 2, 3, 4, 5, 6, 7, 8 and 14.

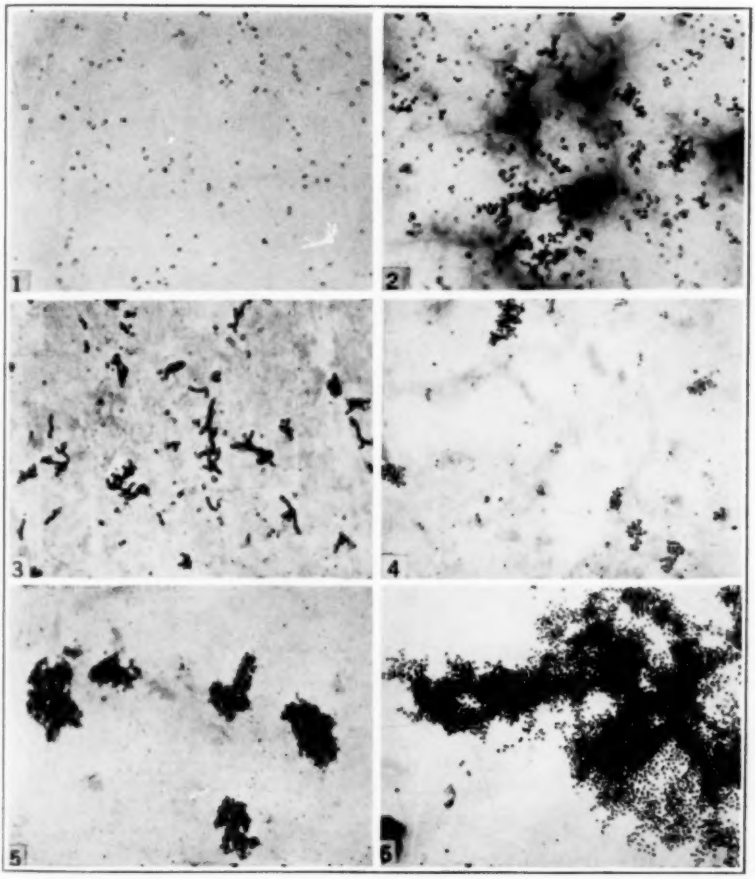

FIG. 1.—The agglutinin test. *1*, Negative agglutinin test; *2*, 1 plus; *3*, 1 to 2 plus; *4*, 2 plus; *5*, 3 plus; *6*, 4 plus.

in 107 patients, 5 of whom died. In 87 the initial test was made before the eighth day of illness; 34 reacted positively to this initial test, on an average of the fifth day of the disease. Eleven of these early reactors to homologous polysaccharide were tested to several heterologous types, and 10 of the 11 reacted to one or more types. From this finding, and from the clinical observation that nearly all of these 34 patients were still critically ill (with high fever and severe toxicity, several with persisting bacteremia) at the time the positive test was obtained, we can conclude that, so far as immunity or increased resistance to the pneumococcus is concerned, these

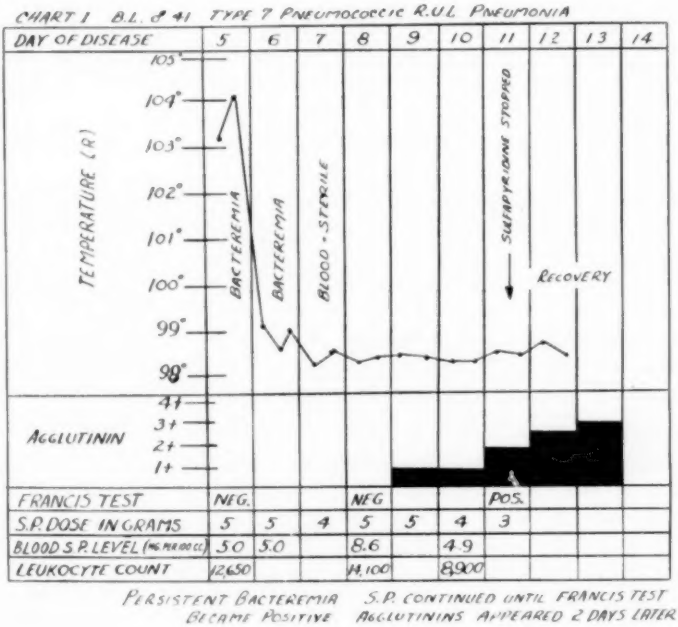

CHART 1.

were "false" positive tests. Fifty-three patients of the 87 tested during the first week of their illness reacted negatively to the initial test. Ten of these remained negative through an average of the fourteenth day of their illness. Two of the 10 patients died. Six of the remaining 8 patients developed a 3 to 4+ agglutinin, and all 8 showed evidence of complete recovery from pneumonia by the end of the second week of the disease. We believe, therefore, that these can be called "false" negative tests. Seven of the 8 were negroes. The character of their skin may account for their failure to exhibit a positive reaction to the injection of the capsular polysaccharide. Four of these patients were skin tested to heterologous

types as well as the homologous type. All reacted negatively. The remaining 43 patients tested during the first week of their illness had an initial negative Francis test, but when it was repeated later in the course of the disease, it reacted positively. In 34 of these patients, agglutinin tests were done simultaneously. The first positive Francis test appeared on an average of 2 days before the agglutinin test became strongly positive (see Chart 1).

For purposes of comparing further the Francis and Sabin tests, an analysis of the tests done day by day was made. Table 3 illustrates the results of this analysis. It indicates that the propor-

TABLE 3.—ANALYSIS OF DAY-BY-DAY RESULTS OF TESTS.

Day of disease:	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13+.	Tot.
Total Francis tests .	2	8	27	31	26	30	47	28	32	21	18	24	18	312
No. positive . .	0	2	11	17	18	17	30	16	20	12	10	11	10	174
Total agglutinin tests	2	17	39	53	64	69	97	90	61	63	56	46	62	719
No. 3 or 4+ . .	0	0	1	2	5	7	15	27	25	30	21	15	28	176
Agglutinin tests:														
Average reaction	0	0.5	1.1	1.0	1.3	1.4	1.5	2.0	2.2	2.5	2.3	2.3	2.5	

tion of positive to negative Francis tests during the first week of pneumonia was much higher than the proportion of strong (3 to 4+) to weak (0 to 2+) agglutinin tests. Prior to the eighth day of the disease, the average reaction of agglutinin tests was always 1.5+ or less. After the eighth day it was always more than 2+.

Table 4 analyzes 102 patients given the Francis test according to whether or not they were complicated. In those patients whose Francis test was initially negative, and later became positive, there was a significant difference in the duration of illness prior to the

TABLE 4.—RELATION OF COMPLICATIONS TO RESULTS OF FRANCIS TEST.

	No. of cases.	Average day of disease Francis test first positive.	Patients with initial positive Francis test.	Change from − to + occurred in	
				No. of patients.	On day.
Uncomplicated cases . .	51	7.5	28	15	8.2
Complicated cases . . .	51	8.9	23	21	10.0
Totals and averages .	102	8.2	51*	36*	9.2

* These totals include patients whose initial test was performed later than the seventh day of their illness.

first positive Francis test. In the complicated cases, the average appearance time of a positive Francis test was 2 days later than in the uncomplicated cases, as compared to a difference of 4 days noted with the agglutinin test (see Table 2).

Summarizing the studies on the Francis test, we observed: 1, that 40% of the patients tested during the first week of the disease gave a "false" positive reaction, in several instances to heterologous as well as the homologous type; (2) that approximately 10% gave a "false" negative reaction through the fourteenth day of illness; and 3, that a change from negative to positive Francis test was

indicative of increasing resistance or active immunity to the pneumococcus. Such a change preceded the development of a significant agglutinin reaction by an average of 2 days, and was delayed for only 2 days by complicating factors.

To understand more fully the factors which influence the development of a strong agglutinin test, we tried to determine why 11 patients failed to develop good agglutinin by the end of the second week of the disease. Four had pneumonia due to Type 7, 3 to Type 1, and 1 each to Types 2, 19, 20 and 23. Of the 11, bacteremia occurred in 4 and confirmed the sputum typing, and in 3 others (one 7, one 1, and the one Type 2), the Francis test changed from negative to positive, which is supportive evidence that the type recovered from the sputum was the etiologic organism of the pneumonia. We cannot feel so sure of the etiology in the other 4 patients, but probably it was correct.* Eight of the 11 were complicated; average age was 41 years.

For purposes of comparison, we analyzed the records of 17 patients whose 3 to 4+ agglutinin test did not develop until the twelfth day, or later. Type incidence of this group did not resemble that of the group of 11 patients who failed to develop strong agglutinin. There were 8 with Type 2, 4 with Type 1, 2 with Type 8, and 1 each with Types 3, 7, and 14. Thirteen of the 17 were complicated; average age was 40 years.

We are forced to conclude that in these 11 patients, no satisfactory explanation for their failure to develop strong agglutinin could be found. In those 7 who had either bacteremia or a change in Francis test from negative to positive, perhaps a strong agglutinin would have been found if the patients were followed longer than an average of 14 days. For practical purposes, however, we have called these 11 cases "false" negatives, amounting to 10% of all cases

* That errors in typing may be responsible for failure to obtain a strong agglutinin test or a positive Francis test in an occasional patient is suggested by 2 of our cases. In 1, the initial sputum analysis yielded Type 15 alone. In the course of another investigation, a throat swab culture was made on the ninth day of illness, and was reported 2 days later as containing a predominance of Type 8 pneumococcus, and a few Type 14 and Type 15. This patient had failed to develop more than a 1+ agglutinin to Type 15 up to the twelfth day, but his Francis test to Type 8 was positive and the agglutinin for Type 8 was 4+; Francis test and Sabin test for Type 14 were both negative. In another patient, because the sputum was inadequate for direct typing, a mouse was inoculated. This yielded a mixture of Types 2, 8 and 18 pneumococci. Accordingly this patient was followed with daily Francis tests for Types 2 and 8, and with agglutinin tests for all three types. The Francis test for Type 8 changed from negative to positive on the ninth day and the agglutinin for Type 8 became 4+ on the thirteenth day. Both Francis and agglutinin tests for Type 2 and the agglutinin test for Type 18 remained negative. In both these cases, Type 8 pneumococci were etiologic. This has made us more critical of the view to which we formerly subscribed that when sputum yields more than one type of pneumococcus, the more virulent type is most likely etiologic, and so-called carrier types are unlikely to be the causative organism. Type 8 is such a carrier type; Types 2 and 14 are not; Types 15 and 18 may be. When the blood culture is negative and lung puncture is not indicated, it is impossible always to determine the etiologic type, but development of agglutinin and a change from negative to positive Francis test establishes the etiologic diagnosis.

tested. This compared with 10% "false" negatives with the Francis test.

Summary. One hundred and ninety-two patients with pneumococcus pneumonia were studied with either the agglutinin test or the skin test with pneumococcus capsular polysaccharide, or both. Of these, 157 were treated with sulfapyridine alone, and, therefore, constitute a good group in which to study the development of active immunity. In 151 patients in whom the agglutinin test was carried out, it was found that 90% of patients followed to the end of the second week of their illness developed strong agglutinin specific for the type of pneumococcus causing their pneumonia. In the 10% who failed to develop good agglutinin, no satisfactory explanation could be found. These cases were, therefore, called "false" negatives. In those patients who were more seriously ill, there was a delay in the development of strong agglutinin, but when it appeared, it was of the same magnitude as in uncomplicated cases. In 107 patients the Francis test, with the pneumococcus capsular polysaccharide, was performed. Of 87 patients so tested during the first week of their illness, 40% gave "false" positive reactions and 10% gave "false" negative reactions through the fourteenth day of illness. In the remaining 50% of the patients tested in the first week of their illness, an initially negative skin test with capsular polysaccharide was found to become positive later in the course of the disease. The skin test became positive on an average of 2 days before the agglutinin test. The severity of the illness did not delay the development of a positive Francis test as long as it did a strong agglutinin test.

Mention is made of 2 interesting cases in which the etiologic diagnosis depended on the Francis and agglutinin tests.

Conclusions. We conclude from our observations that the agglutinin test is a reliable index to the development of increased resistance to the pneumococcus in the course of pneumonia. It is such a simple test that it may be readily used as a control for sulfapyridine treatment. It rarely becomes positive before the eighth day of the disease; and since in complicated cases it is delayed until the twelfth to thirteenth day, it is particularly important that sulfapyridine be continued longer in such cases. Relapse and late septic complications may be prevented if this is done.

The Francis test is reliable in only 50% of the cases (with the polysaccharide solutions we used). The solutions of polysaccharide are available only for the more common types.

A change from negative to positive Francis test occurs on an average of 2 days before the agglutinin test becomes strongly positive. When this change is noted, it is probably safe to decrease the dosage of sulfapyridine, and to discontinue it 2 days later.

As we concluded in our previous paper, recovery in pneumonia treated with sulfapyridine depends on three factors: an adequate early leukocytosis, an adequately maintained sulfapyridine blood

level, and development of active immunity by the patient for the type of pneumococcus causing his pneumonia. The agglutinin test is a simple, inexpensive, rapid method for determining when active immunity develops.

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DIAGNOSIS OF THE CAUSE OF AN OBSTRUCTIVE JAUNDICE BY MEANS OF THE BLOOD PICTURE.

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For many years various hematologic tests have been employed for the differential diagnosis between obstructive and hemolytic forms of jaundice. In this connection the fragility of the erythrocytes, the number of the reticulocytes and the character of the van den Bergh reaction are most important. In the cases of jaundice which are found to be due to an obstruction to the outflow of bile, the question then arises as to the cause of this obstruction, and precise diagnosis may here be of considerable importance, as on it depends the advisability of operation.

In the course of carrying out complete and detailed hematologic examinations on patients with obstructive jaundice it occurred to us, because of the marked differences in the blood pictures which we encountered, that one might gain information of diagnostic value as to the cause of the obstruction. We therefore followed such cases until a definite diagnosis was established, and compared the blood pictures in different patients in which the obstruction was due to the same cause. In doing this it soon became apparent that certain changes in the blood were met with almost constantly in those cases having the same etiology. We then ventured to offer a diagnosis as to the cause of the obstruction at the time of the blood study, and found in a large percentage of cases our conclusions turned out to be correct. While this was encouraging, we felt the actual diagnostic value of the information obtained could only be determined if precise rules of diagnosis were laid down and all of a series of cases submitted to them. The results of this investigation are reported below.

Before proceeding with the collection of such a series of cases, it was, of course, necessary to decide upon certain criteria for inclusion of the cases in this group. This was particularly important because obstructive forms of jaundice vary greatly in degree and occur commonly as purely secondary or terminal complications. It was therefore decided that no case would be included in which

the hyperbilirubinemia was less than 1.5 units (0.75 mg. per 100 cc.) or in which the van den Bergh test did not present a strongly positive prompt direct reaction. Moreover, of the cases conforming to this type and degree of bilirubinemia we excluded all those occurring in pregnancy, the newborn and children, acute infections, extensive metastatic involvement of the liver, anemias and other blood dyscrasias, and cases in which the jaundice was distinctly of secondary importance. In other words, we confined the series to persons presenting themselves with a history of jaundice which proved to be of obstructive type and in which the question of the cause of the jaundice naturally arose. Seventy consecutive cases constituted the series.

The hematologic examinations consisted of our usual routine blood studies plus the Takata-Ara test and estimation of the bilirubinemia by means of the Evelyn photoelectric colorimeter. Blood was taken from the patient between 10 and 12 o'clock in the morning and a certain amount of special care was used to obtain very accurate figures for the total and differential white blood cell counts. As usual in our blood studies, the number per cubic millimeter of *each type of white blood cell* was determined. These figures are most important and much more valuable for hematologic diagnosis than the simple relative values given by the percentages.

Although there are a great many possible causes of obstructive jaundice, almost all cases which meet the criteria laid down above consist of one of four conditions. These are malignancy of the pancreas or biliary channels, cholelithiasis, catarrhal jaundice and cirrhosis of the liver. It is the differential hematologic diagnosis between these four diseases with which we are particularly concerned and we shall therefore first present the more or less specific blood changes which we found to occur in each.

In obstructive jaundice due to *malignancy* within or pressing upon the bile channels, the sedimentation velocity of the blood rises. In the majority of cases it reaches figures of over 20 mm. for the first hour, and in fact is often over 30 mm. We employ the method recommended by Wintrobe and, of course, correct for any abnormality in the volume of packed cells. Similarly high readings in the sedimentation velocity may be met with in stone, provided there is an associated relatively acute cholecystitis, and sometimes in advanced cirrhosis, but never to our knowledge in uncomplicated catarrhal jaundice. Should the growth be small with little invasion and destruction of tissue, the increase may be less and the figure after correction lie between 10 and 20 mm. The white blood cells, as a rule, show a certain amount of leukocytosis. This may be only slight or quite marked. The rise is due to an increase in the neutrophils while the lymphocytes fall. This decrease in lymphocytes is a very striking feature in many cases. We have come to use the figure 2000 per c.mm. as our normal base line and consider any count below this as a lymphopenia or at least not a lymphocytosis.

Figures below 1000 are not uncommon. Marked degrees of lymphopenia have never been found in catarrhal jaundice or in cholelithiasis unless there is an associated acute gall bladder condition. It may occur, however, in cirrhosis with anemia and general reduction in all the white blood cells.

In obstruction of the common duct by *stone*, we have found there occurs a lymphocytosis and only a slight rise in the sedimentation velocity. The increase in the total number of lymphocytes may be small but frequently is quite marked with figures around 3000 per c.mm. This is probably due to the low-grade cholecystitis which is usually present. On the other hand, as mentioned above, if there is an associated acute gall bladder infection, the sedimentation velocity rises and the changes in the white blood cell conform to those met with in acute inflammatory processes, namely, a rise in neutrophils with reduction in lymphs.

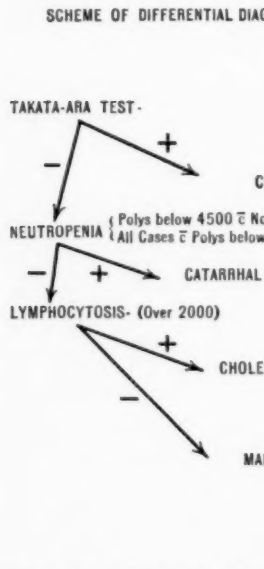
In *catarrhal jaundice* the hematologic findings are, as a rule, distinctly different. The most outstanding feature is the marked reduction in neutrophils. As the base line for these cells we take 4500 per c.mm. and have found in this condition that they often fall below 3500, with figures from 2000 to 2500 as not uncommon. There is usually a moderate rise in lymphocytes. In addition the blood shows an increased viscosity with relatively high count of erythrocytes and a decreased or normal sedimentation velocity. Only in the rare cases where this condition goes on to a hepatitis or pancreatitis do we find this picture appreciably altered.

In many cases of *cirrhosis* the hyperbilirubinemia is not of the type met with in obstructive jaundice; however, cases do occur in which the van den Bergh test gives a strongly positive prompt direct reaction and differential diagnosis from malignancy and other conditions may be difficult. The changes in the morphologic elements of the blood in this disease are subject to great variation; however, we fortunately have a serologic test in the Takata-Ara reaction which allows us to identify the condition from other members of the group. While it is well recognized that this reaction is not pathognomonic of cirrhosis and may at times be negative in even advanced cases, we have found it extremely valuable and quite trustworthy as a diagnostic aid.

From the results of our studies on a number of these cases, a scheme of differential diagnosis has been drawn up. This purposely confines itself to the hematologic evidence and was made as simple as possible in order that our series might be submitted to a precise diagnostic test. The scheme is reproduced herewith diagrammatically in the accompanying chart and works out as follows: Once a case is established by the other hematologic evidence as that of an obstructive form of jaundice and found to fulfill the criteria outlined above for inclusion in the series, the results of the Takata-Ara test are first considered without regard to any changes in the white blood cells. If this test is positive, the case is imme-

diately diagnosed as a cirrhosis. Faint or plus-minus reactions are considered negative. In our experience, while borderline results are met with, in peri-insular cirrhosis the findings are usually so strongly positive that no question arises.

If the Takata-Ara test is negative, the number of neutrophils per cubic millimeter and the sedimentation velocity are next taken into consideration. If the neutrophils fall below 3000 per cubic millimeter, regardless of the changes in sedimentation velocity, the case is diagnosed catarrhal jaundice. However, if the neutrophils are between 3000 and 4500 it is only given this diagnosis in the presence of a normal sedimentation velocity, that is, not over 10 mm. in the first hour after correction for the volume of packed



RESULTS IN 70 CONSECUTIVE CASES

	NUMBER OF CASES	POSITIVELY CORRECT	PROBABLY CORRECT	TOTAL	PERCENT
CIRRHOSIS:-	8	7	1	8	100
CATARRHAL JAUNDICE:-	16		15	15	94
CHOLELITHIASIS:-	10	4	5	9	90
MALIGNANCY:-	36	26	3	29	81
TOTALS:-	70	37	24	61	87

CHART 1.—Diagnosis of the cause of obstructive jaundice by the blood picture.

cells. All cases therefore with neutrophils over 4500 and those cases with 3000 to 4500 neutrophils plus increased sedimentation velocity are considered negative to this diagnosis.

Should the findings fail to allow for either a diagnosis of cirrhosis or catarrhal jaundice, the number of lymphocytes per cubic millimeter becomes important. If these are over 2000, the jaundice is usually due to cholelithiasis; if, on the other hand, the lymphocytes fall below this figure, it is placed in the group of malignancy. In the cases of jaundice due to stone, as a rule, the lymphocytes rise considerably, while in cancer they often fall below 1000. There are therefore comparatively few cases in these two groups in which the figure is close to the borderline of 2000. In the final or malignancy group, which includes all cases which have not allowed for

a diagnosis of cirrhosis, catarrhal jaundice or stone, one also finds some cases of acute cholecystitis. We found it impossible to separate these by any specific hematologic finding from malignancy, though other clinical evidence usually allows for a ready recognition.

It should be quite obvious that the scheme of differential diagnosis described above must be followed precisely and in the order given, for it is so drawn up that only under those conditions will it be of value in giving information as to the cause of the jaundice.

In the second part of the accompanying chart are given the results which were obtained in the application of the scheme of diagnosis to 70 consecutive cases of obstructive jaundice examined by us which conformed to the specifications laid down above for inclusion in the series. In all of these cases where a positive diagnosis was not obtained by operation, biopsy or autopsy, a special attempt was made to confirm the clinical diagnosis by following up the case after it left the hospital.

In the series of 70 cases, a positive Takata-Ara test was obtained 8 times. Seven of these 8 cases came to autopsy and the diagnosis of peri-insular cirrhosis was confirmed. The other case died at home and no postmortem examination was done. However, the clinical findings and course were always quite typical of this disease and no doubt ever arose as to the diagnosis. This gives a total of 8 correct out of 8 (100%).

Sixteen cases showed the neutropenia and sedimentation velocity to put them in the group of catarrhal jaundice. Of these, 7 had less than 3000 neutrophils per cubic millimeter, while 9 had over 3000, but less than 4500 neutrophils, with normal sedimentation velocity. All of the cases with neutrophils below 3000 were diagnosed catarrhal jaundice clinically on leaving the hospital, and follow-up of these patients has failed to show anything to alter this opinion. One underwent exploratory laparotomy while in the hospital but no other cause for the jaundice was disclosed. Of the 9 cases with neutrophils between 3000 and 4500 and normal sedimentation velocity, 4 were discharged from the hospital with a definite diagnosis of catarrhal jaundice, 4 were considered uncertain but probably catarrhal jaundice. The remaining case was later operated on and a silent stone found in the common duct with a small thickened gall bladder. Follow-up of the other cases showed no reason to alter the diagnosis. This gives a total of 15 out of 16 probably correct (94%).

Of the remaining cases, 10 showed over 2000 lymphocytes per cubic millimeter. The sedimentation velocity in these patients varied from normal to rapid. In 4, stone was found in the common duct at operation. Four others were diagnosed jaundice due to stone, but not operated upon. One was operated on and a large dilated gall bladder removed. No stone was present in the duct, but it was concluded that the jaundice had been caused by a stone

which had passed. The remaining case proved at operation to have a carcinoma of the head of the pancreas. This gives a total of 9 out of 10 probably correct (90%).

The remaining 36 cases had less than 2000 lymphocytes per cubic centimeter and consequently fell into the final or malignancy group. In many the differential white blood cell count showed a marked lymphopenia with less than 1000 per cubic millimeter. Of the 36 cases, the diagnosis of carcinoma was positively confirmed by operation, biopsy or autopsy in 26. In 3 other cases the diagnosis of malignancy was felt to be quite certain, but there was no operation or autopsy. Four cases had acute gall bladder conditions with cholelithiasis. In these there was an increase in the total white blood cells to around 10,000, with the typical differential picture of acute infection (high neutrophils and low lymphocytes) and rapid sedimentation velocity. Of the 3 remaining cases in this group, 1 was operated upon and the obstruction of bile was found due to a fibrosis of the common duct; another was discharged with a probable diagnosis of a catarrhal jaundice which had gone on to a chronic cholangitis; and the third, who refused operation, was sent home without any definite conclusion as to the cause of jaundice being reached. This patient may have had a cancer but we were unable to get any further information through follow-up sources. In this group the diagnosis of malignancy was positively correct in 26 and probably correct in 3, a total of 29 (81%).

Summarizing the complete series of 70 cases one finds the diagnosis positively confirmed by operation, biopsy or autopsy in 37 and probably correct in 24, which includes 15 cases of catarrhal jaundice. This makes a total of 61 out of 70 (87%) in which one feels quite justified in concluding that the hematologic diagnosis according to the scheme presented has given the correct diagnosis of the cause of the obstructive jaundice.

In a number of instances the hematologic diagnosis was found eventually to be correct in cases where the other clinical findings had led to erroneous conclusions. As an example, we had the case of a large fleshy woman of 65 years who was believed to have a carcinoma of the head of the pancreas. A large, tense, dilated gall bladder was apparently palpable. The hematologic findings were those of catarrhal jaundice. Laparotomy was performed and the mass was found to be a Riedel lobe of the liver. She made an uneventful recovery.

In another case, a 50-year-old male was suspected of having malignancy because of the duration and intensity of the obstructive jaundice with marked hyperbilirubinemia. The Takata-Ara test was positive and autopsy revealed a peri-insular cirrhosis. On one occasion where the hematologic findings were those of malignancy, the abdomen was opened and no cause for the jaundice could be found. Autopsy later revealed a small intrahepatic carcinoma at

the junction of the hepatic ducts. Several other interesting examples of the valuable information given by the blood findings might be included.

It is beyond the scope of this paper to enter into a theoretical discussion of the possible explanations for the various blood pictures presented. It is doubtful if it could lead to anything more than hypothetical statements. The scheme of diagnosis presented is essentially an empirical trick based on the findings in a large number of cases. Until our knowledge of the causes for the various changes met with increases, it is better to accept it as such.

Conclusions. A scheme for the differential diagnosis of the causes of obstructive jaundice by means of certain hematologic findings is presented. By this method jaundice due to malignancy, jaundice caused by stone, catarrhal jaundice and cirrhosis can usually be readily identified. In a series of 70 consecutive cases the diagnosis based on this evidence was found to be positively or most probably correct in 87%.

THE RELATION OF PHOSPHORUS TO FAT AND GLUCOSE METABOLISM IN SPRUE.

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It is the currently accepted view that the sprue syndrome is caused by faulty absorption from the intestinal tract,[3,5,12,13,16,19] though the cause of this defective absorption is not known. The sprue patient absorbs proteins normally, but fats and carbohydrates are poorly absorbed, leading often to secondary deficiencies of vitamins, calcium, phosphorus, and a hematopoietic factor. There are sound reasons for thinking that the absorption of many foodstuffs depends upon phosphorylation,[23] the importance of phosphorus in the intermediary metabolism of carbohydrates is well established, and there is much evidence that it is involved, likewise, in the intermediary metabolism of fat.[18] It was thought, therefore, that a study of the phosphorus metabolism in sprue during the absorption of oil and glucose might give some further information on absorption and metabolism in this condition. Furthermore, it was hoped that the study might give some evidence in support or refutation of the theory proposed by Verzar[22] that the underlying physiologic defect in sprue is a breakdown in the phosphorylating mechanism of absorption.

In the course of a study on the effects of the ingestion of phospholipid upon metabolism[15a] it was found that after the ingestion of

olive oil by normal humans there is a lowering of the serum inorganic phosphorus and decreased urinary phosphorus excretion. This phenomenon has been reported after the ingestion of carbohydrates[2,4,6,8,14,20] where it is thought to be due to a mobilization of phosphorus in the muscles for sugar metabolism, but it does not

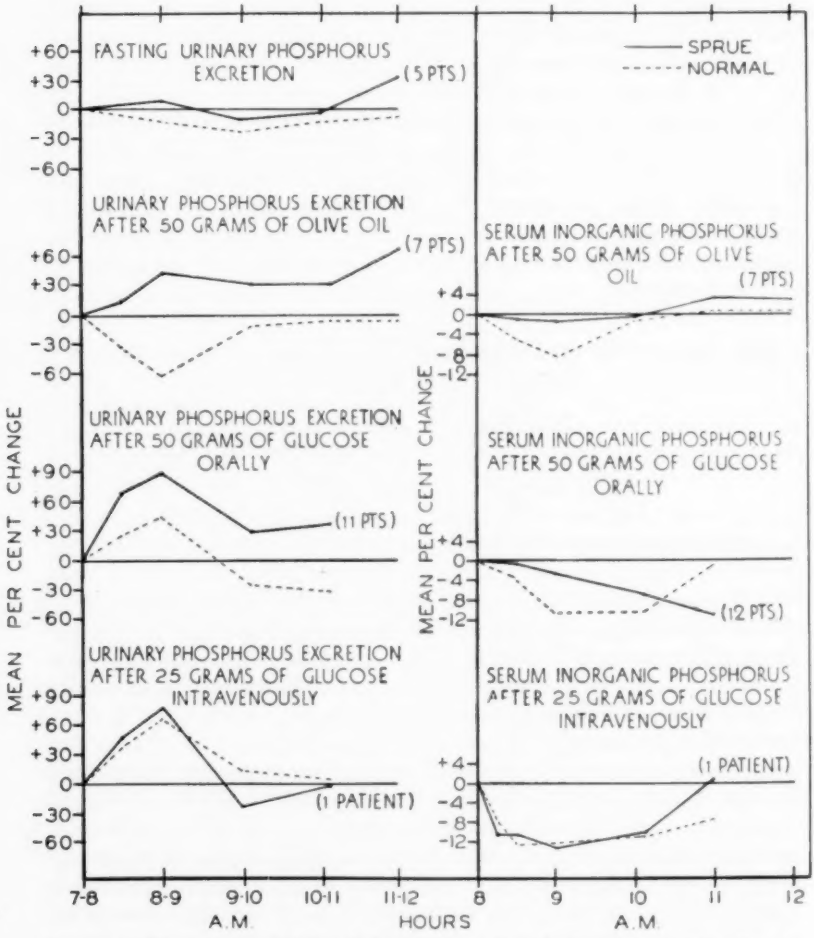

CHART 1.—The relation of fat and glucose absorption to phosphorus metabolism in normal persons and in sprue.

occur after the ingestion of proteins,[9,10,17] in which case, on the contrary, there is an increase in urinary phosphorus excretion.

We then investigated more completely the changes in serum phosphate and rate of phosphorus excretion after the administration of oil and glucose to normal humans and have reported the results elsewhere.[15b] Finally, we have made the same observations on

sprue patients and have found considerable variation from the normal after the ingestion of the metabolites, but normal results after their intravenous injection. The respiratory quotient was also determined on sprue patients after meals of oil and glucose.

Experimental. All experiments were conducted in the morning approximately 15 hours after the last meal. At 7 A.M. the subjects voided and received a glass of water. Just before 8.00 they again voided and immediately after were given the test meal and a glass of water. Blood and urine samples were taken, and a glass of water given at 8.30, 9.00, 10.00, 11.00 and 12.00. Serum and urinary phosphorus were determined according to the method of Fiske and Subbarow.[7] The respiratory quotient was determined by collecting the exhaled air for 5 minutes in a Douglas bag and analyzing it in an Haldane apparatus.

Discussion. The mean per cent changes are reviewed in the chart. The number of experiments vary from 5 for the fasting urinary phosphorus excretion to 13 for the effects of ingested glucose, except that only 1 intravenous glucose tolerance test was performed. The mean values are very representative of the individual experiments. The normal changes[15b] are given for comparison.

The normal phosphorus changes in sprue after intravenous glucose and the close parallel between the degree of elevation of the respiratory quotient and blood sugar after oral glucose (Table 1) are evidence that the sprue patient can metabolize glucose normally after it is in the blood. Consequently, the delayed fall observed in serum phosphorus after the ingestion of glucose by these patients can only be explained on the basis that the sugar reaches the blood stream abnormally slowly, that is, is very slowly absorbed. This does not support Thaysen's theory that the low blood sugar curve is due to abnormally rapid assimilation of the absorbed glucose by the starved tissue.[21]

TABLE 1.—BLOOD SUGAR AND RESPIRATORY QUOTIENT AFTER THE INGESTION OF 50 GM. OF GLUCOSE BY SPRUE PATIENTS.

Hours after sugar.	P. L.		P. L.		L. M.		L. J.*		W. S.		A. B.	
	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.	Bl. sug.	R. Q.
Fasting	78	0.777	85	0.732	72	0.770	98	0.727	70	0.799	79	0.722
0.5	81	0.806	103	0.875	72	0.835	104	0.779	83	0.790	78	0.753
1.0	91	..	115	0.843	77	0.874	178	0.845	105	0.862	84	0.726
2.0	88	0.783	103	0.876	82	0.861	103	0.800	121	0.923	87	0.774
3.0	87	0.758	89	0.848	73	0.859	91	0.828	93	0.867	95	0.778

* Patient in remission.

Similarly, the delayed fall in respiratory quotient (Table 2), the correspondingly slight increase in blood fats[1,11] and the failure of any serum phosphorus response after oil ingestion parallel the conditions after glucose ingestion and make it evident that here, too,

the abnormal phosphorus changes result from the failure of the metabolite to reach the blood at a normal rate.

TABLE 2.—THE RESPIRATORY QUOTIENT AFTER THE INGESTION OF 50 GM. of OLIVE OIL BY SPRUE PATIENTS.

Hours after oil.	L. J.	L. J.	W. S.	W. S.	A. B.
Fasting . . .	0.827	0.776	0.790	0.956	0.748
0.5	0.730	0.792	0.812	0.961	0.743
1.0	0.749	0.770	0.838	0.897	0.763
2.0	0.740	0.716	...	0.813	0.805
3.0	0.746	0.752	0.870	0.803	0.755
4.0	0.731	0.730	0.755	0.841	0.703

The explanation for the increase in the rate of phosphorus excretion in sprue during absorption is not so obvious. However, since it is true that the phosphorus content of the tissues is increased after the ingestion of oil and glucose[8,155] the presence of food in the intestine may be the stimulus which causes this mobilization. If the food fails to reach the blood, the mobilized phosphorus is excreted.

Summary. 1. Sprue patients do not exhibit the normal fasting diurnal variation in phosphorus excretion.

2. After the ingestion of olive oil by sprue patients there is an increase in urinary phosphorus excretion as compared to a decrease in normals. There is no significant change in serum inorganic phosphorus.

3. After the ingestion of glucose by sprue patients the serum phosphorus decreases much more slowly and the urinary phosphorus excretion is much greater than in normals.

4. The changes in blood sugar, serum phosphorus, and rate of phosphorus excretion after the intravenous injection of glucose are of the same order in normal persons and in sprue patients.

5. These findings, as well as the delayed changes in respiratory quotient after oil and glucose meals, reflect the slow rate of intestinal absorption by the sprue patient.

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THE CENTRAL NERVOUS SYSTEM STIMULANT EFFECTS OF DEXTRO-AMPHETAMINE SULPHATE.

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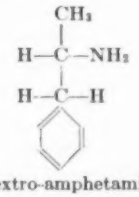
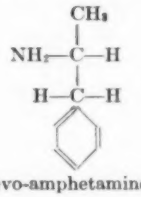
The central nervous system stimulant effects of amphetamine (racemic α-methylphenethylamine or phenisopropylamine, benzedrine, S.K.F.) were noted by Alles[1a] in its awakening effects on anesthetized animals and in its insomnia-producing effect in man. Therapeutic use of the central effects of amphetamine was first made by Prinzmetal and Bloomberg.[14] A large literature has since accumulated verifying these observations and amplifying knowledge with regard to the effects of amphetamine manifested as a result of its stimulant actions upon central nervous system mechanisms.

Amphetamine is a racemic compound and is composed of equal parts of the optically active dextro- and levo-isomers. By suitable means amphetamine may be resolved into its two optically isomeric components which may be represented by the structural formulæ:



Dextro-amphetamine.



Levo-amphetamine.

These two compounds differ in their asymmetry about the second carbon atom on the side chain, just as dextro-ephedrine differs from dextro-pseudoephedrine, or as levo-ephedrine differs from levo-pseudoephedrine. However, the structures of ephedrines and pseudoephedrines each contain two asymmetric centers which also lead to differences in chemical and physical properties other than in their optically rotatory powers.

A study of the comparative physiologic actions of the optically isomeric amphetamines has been reported by Alles[1b] who found their activities upon peripheral nervous system mechanisms to be closely similar. Their central nervous system stimulant effects differed considerably, however, and the dextro-isomer was found to be more active than the racemic or levo-isomers. In experiments on man, following oral administration, the stimulant and insomnia-producing effects of the dextro compound were 2 to 4 times greater

than with the levo compound. Trevan[19] has reported that the analeptic effect of the dextro-isomer is greater than that of the levo-isomer for mice anesthetized with paraldehyde.

It therefore seemed important to determine the effectiveness of dextro-amphetamine in clinical conditions where the central nervous system stimulating effects of racemic amphetamine has been found to be of therapeutic value. From the clinical standpoint, comparison of the dextro and racemic compounds is of chief interest, but comparison of the dextro and levo compounds was also carried out to some extent because of the theoretical interest in the valuation of the ratio of their activities. All compounds were used in the form of their sulphate salts, and administered in water solutions of various concentrations so that the patients received dosages constant in volume and appearance. The subjects were not told what compound they were receiving, and kept accurate daily notes of its effect. By repeated trials of various concentrations of the different isomers, an estimation of the relative effectiveness of each compound was determined. The patient's response was generally first standardized with the racemic sulphate, then the dextro and levo sulphates were substituted and compared. Such a comparative study generally took from 2 to 4 months for each patient, as each compound at each dosage level was usually maintained for a week or more, and repeated in all cases, before drawing conclusions.

Narcolepsy. The central nervous system stimulating effects of amphetamine sulphate were used for treatment of this disease by Prinzmetal and Bloomberg[14] and their observations have been confirmed.[15,18,20,21] Freedom from attacks of sleep and practically complete relief from cataplexy are obtained when suitable doses are given. Although narcolepsy is a rare disease, it is an important one for the study of the central effects of this type of drug compound. The beneficial actions are so definite and striking that it is possible to evaluate the relative activities of related compounds with some degree of precision. We have been able to study the effects of the several compounds of interest in 6 cases of narcolepsy. In all instances dextro-amphetamine was found to be much more effective than racemic amphetamine. A summary of the dosages found equally effective is given in Table 1. The average amount of dextro-amphetamine sulphate for all 6 cases was 20 mg. per day, compared with 38 mg. of racemic amphetamine sulphate, or 60 mg. of levo-amphetamine sulphate.

Postencephalitic Parkinson's Disease. The effectiveness of amphetamine sulphate in treatment of certain symptoms of patients with postencephalitic Parkinson's disease was observed by Solomon, Mitchell and Prinzmetal.[17] They found that its use in conjunction with stramonium is beneficial in most cases, causing an increase in energy and a decrease in drowsiness and oculogyric crises in all

such cases. In about two-thirds of benefited cases there were decreases in both rigidity and tremor. Similar results have been reported by others.[4,6,9,16] The effects of the amphetamine isomers have been studied by us in 4 cases of postencephalitic Parkinson's disease.

Dextro-amphetamine was found to be of therapeutic benefit in all 4 cases, and a comparison of the relative effectiveness in 2 of the patients showed dextro-amphetamine to be more effective than similar doses of racemic amphetamine or of levo-amphetamine (Table 1).

TABLE 1.—COMPARISON OF EFFECTS ON NARCOLEPSY, POST-ENCEPHALITIS IN PARKINSON'S DISEASE AND POSTURAL HYPOTENSION.

Narcolepsy.

Case.	Sex.	Age.	Daily sleep attacks without medication.	Daily attacks of cataplexy—no medication.	Effective daily dose. Dextro (mg.).	Racemic (mg.).	Levo (mg.).
1	F	36	4–6	4–6	28	45	70
2	F	34	4–6	1–2	26	52	
3	M	22	4–6	Occasional	25	50	
4	F	30	4–15	None	20	40	80
5	F	27	3–4	Occasional	12.5	25	50
6	M	25	1–3	Occasional	10	20	40
Average for cases of narcolepsy					20	38	60

Post-encephalitic Parkinson's Disease.

Case.	Sex.	Age	Symptoms.	Effective daily dose. Dextro (mg.).	Racemic (mg.).	Levo (mg.).
7	M	31	Drowsiness, rigidity, tremor and oculogyric crises	25	40	50
8	M	54	Tremor, rigidity, and oculogyric crises	20	40	
			Postural Hypotension.			
9	M	34	Weakness, dizziness upon assuming the upright position . .	5	10	20

Postural Hypotension. One of the authors of this paper[13] reported that amphetamine sulphate relieved the symptoms of a patient with postural hypotension, and others[3,8] have confirmed these results. It was observed that, although the compound relieved the symptoms of the disease, it had but little effect on the fall in blood pressure on assuming the upright position. Paredrine hydrochloride, a compound which tended to stabilize the blood pressure but which has no central nervous system stimulating effect, had little or no effect on the symptoms. It therefore appeared that the beneficial effect of amphetamine sulphate is not primarily due to a rise in blood pressure, a suggestion occasionally offered. In 1 carefully studied patient with postural hypotension (Case 9), the dextro compound proved to be twice as effective as the racemic

compound and 4 times as effective as the levo compound in alleviating his symptoms (Table 1). The relief of the symptom of dizziness had no obvious connection with the effect of the drugs on his blood pressure.

Effect on Dizziness. We have observed that the central nervous system stimulating action of these compounds was helpful in alleviating dizziness in several patients without obvious organic disease, though most of these subjects had hypotension. Benefit was also obtained in 2 patients with Ménière's syndrome. The improvement in these patients was not associated with an elevation of blood pressure. Indeed, paredrine hydrochloride, a compound with no central nervous system stimulating effects but with more marked pressor effect, has no therapeutic effect in these subjects. The mechanism of relief is therefore similar to that found in patients with postural hypotension. Because of the difficulties of adequate control, a comparison of the various isomers of amphetamine was not made in this group of patients.

Depressed States. Amphetamine sulphate was found to be useful in certain cases of depression by Guttman[7] and by Meyerson.[10] Their observations have been confirmed and extended by others.[2,11,22,23]

An evaluation of central nervous system stimulating drugs in patients with depression is extremely difficult to perform because of the marked spontaneous fluctuations in this condition. We have found that dextro-amphetamine had therapeutic benefit and usefulness in 4 patients with simple depressions. The following case, referred by Dr. Emanuel Libman of New York City, showed a greater benefit from the dextro compound than with larger doses of the racemic amphetamine.

A 54-year-old white male had had periods of depression for about 10 years. The depression was much worse in the morning and would gradually wear off during the morning. The patient worried a great deal about his condition and contemplated giving up the practice of law because of it. He was given 5 mg. per day of racemic amphetamine sulphate with marked improvement in his condition, so that he had no difficulty with his work. After several months, he was given a solution of dextro-amphetamine sulphate. A dosage of 3 mg. of this compound had a greater stimulating effect than 5 mg. of the racemic compound.

Stimulating Effects in Normal Persons. That racemic amphetamine sulphate "stimulates" most normal individuals has been observed by most persons using this drug. There is often a feeling of exhilaration, increased confidence, euphoria, loquaciousness, and insomnia. Nathanson[11] has reported an extensive study of the stimulant effects of racemic amphetamine in normal persons.

A comparison of the stimulating effects of dextro- and racemic amphetamine sulphate was made on 13 normal persons who took 2.5 mg. of the dextro and racemic compounds on alternate days in

solution.* The subjects were all doctors or nurses of the Los Angeles County Hospital. They were not told what compound they were receiving, but were asked to pay attention to the degree of mental stimulation produced.

Of the 13 cases, 12 reported that the dextro compound had a definitely greater stimulating effect than the racemic compound. In only 1 case did the subject experience difficulty differentiating the two compounds. It is of interest that some individuals noticed no effect from 2.5 mg. of the racemic compound, but noticed stimulating effect from the same dose of dextro.

TABLE 2.—COMPARISON OF EFFECTS ON NORMALS.

Case.	Sex.	Dose taken racemic (mg.).	Effects.	Dose taken dextro (mg.).	Effects.
1	F	2.5	Felt less tired	2.5	Greater effect—more pep, loquacity, some sleeplessness that night
2	F	2.5	Felt less tired at end of day	2.5	Less fatigue than with racemic; very thirsty
3	F	2.5	No effect	2.5	Nasal and oral mucosæ very dry; very thirsty for 1 hour afterward
4	F	2.5	No effect	2.5	Very nervous—thirsty; mouth dry for 1½ hours
5	F	2.5	No effect	2.5	No effect
		5.0	No effect	5.0	Slightly nervous—vague stimulation
6	F	2.5	No effect	2.5	Felt more energetic—not so tired
7	M	2.5	More awake for about 1 hr.	2.5	Similar effect, perhaps more awake
		5.0	Slight stimulation	5.0	Mouth dry; vaguely stimulated
8	M	2.5	Mentally more active; no fatigue until late at night	2.5	Excitement; greater mental and physical activity; mouth dry; nervous; moved quickly; garrulous
9	M	2.5	No effect	2.5	No effect
		5.0	No effect	5.0	Hyperexcitable, loquacious, jittery
10	F	2.5	Increased activity—then "let down"	2.5	Less stimulation than with racemic
		5.0	Not conscious of any effect	5.0	Excited, nervous, jittery; dry mouth and very thirsty
11	M	2.5	No effect	2.5	No effect
		5.0	No effect	5.0	Mental lift—less fatigue; moved faster than usual
12	M	2.5	No effect	2.5	Hyperactive and loquacious
13	M	2.5	Slight mental stimulation	2.5	Greater muscular and mental activity; thirsty, better appetite

Pressor Effects. Comparison of the pressor effects in normal persons of the dextro-, racemic and levo-isomers of amphetamine was reported by Alles.[15] Following oral administration of the compounds in doses of 10 and 20 mg. doses, their pressor responses were quite closely the same. In resting persons, usually as little as 10 mg. of the sulphates of these isomers causes a definite pressor response, but some apparently normal individuals may not show definite pressor responses even after administration of 20 mg. of racemic amphetamine.

Pressor studies were systematically carried out with only 2 narcolepsy cases, since such observations have little value unless the

* These observations were made with the aid of Dr. Harvey Lewis.

persons remain at rest throughout the period of observation. Case 1, who had a resting blood pressure level of about 92/70, showed no definite changes in the systolic or diastolic level following 30 mg. of the dextro-, racemic or levo-amphetamine sulphates, although one-half of this amount in single doses of the dextro or racemic compounds exerted marked antisleep effects. Case 4, who had a resting blood pressure of about 100/68, showed no definite pressure changes following 30 mg. of the racemic amphetamine sulphate, although one-half of this amount in a single dose exerted definite antisleep effect.

Discussion. It is of interest that similar results were obtained on all subjects studied. The dextro-amphetamine sulphate proved much more active than the racemic compound in the cases of narcolepsy, postencephalitic Parkinson's disease, postural hypotension, simple depressions, and in normal individuals. Reviewing the entire series, it is possible to make an evaluation of the comparative strength of the various compounds by averaging all cases where a comparison was made. The dextro-amphetamine sulphate is approximately $1\frac{1}{2}$ to 2 times more active than the racemic compound, and 3 to 4 times more active than the levo compound.

Because of the vascular effects of racemic amphetamine it should be used with caution in patients with hypertension and it may precipitate an anginal attack in certain cases of angina pectoris.[12] For an equivalent central stimulant effect, a smaller dose of the dextro-isomer is required and therefore will exert less vascular effect than is obtained with a larger dose of the racemic compound, and its use would seem to be clearly indicated with patients who may derive untoward vascular responses from racemic amphetamine.

It is of interest to note that the lethal dosages for mice of the dextro-, racemic and levo-isomers are closely the same.[16] Therefore, if a given desired result can be obtained from the dextro compound with one-half the dose required of the racemic form, the ratio between the therapeutic and lethal dose is decreased by one-half. Although the ratio of therapeutic to lethal dose would appear to be somewhere between 1:100 to 1:1000 with racemic amphetamine,[5] the further decrease in the ratio may be of some clinical significance.

From these results it would appear that for central nervous system stimulation dextro-amphetamine is a more desirable drug than racemic amphetamine, particularly if there is evidence that the racemic compound does cause undesirable circulatory responses in a given individual. Conversely, it is to be expected that levo-amphetamine would be a more desirable drug than racemic amphetamine when the therapeutic objective is vasoconstriction or other stimulation of peripheral sympathetic nervous system mechanisms.

It seems quite clear from the relation that exists between dextro- and levo-amphetamine that the central nervous system stimulating

effects are unrelated to systemic pressor effects. Paredrine, the para-hydroxy derivative of amphetamine, has greater cardiovascular effects than amphetamine but is without notable effect in stimulating the central nervous system. The failure to note any pressor changes in the narcoleptics, studied at dosage levels sufficient to result in marked antisleep effects, is perhaps more direct proof of the independence of these two effects of amphetamine. That amphetamine has central actions other than on the sleep center is indicated by its causing relief of oculogyric crises in Parkinson's disease and of the cataplexy of narcolepsy.

Conclusions. 1. A study was made of the central nervous system stimulating effects of dextro-, racemic and levo-amphetamine sulphates in subjects with narcolepsy, postencephalitic Parkinson's disease, postural hypotension and simple depression.

2. The central nervous system stimulation induced by these compounds is useful in the treatment of dizziness in certain patients.

3. Comparison of the central stimulant effects of dextro- and racemic amphetamine sulphates was also made on normal individuals.

4. It was found that the central effects of the dextro-isomer are approximately 1½ to 2 times that of the racemic isomer, and 3 to 4 times that of the levo-isomer.

5. The pressor effects of the dextro-, racemic and levo-isomers are closely the same in normal persons.

6. A smaller dose of dextro-amphetamine sulphate can be employed than with the racemic compound for therapeutically useful central stimulant effects with correspondingly less cardiovascular effect and a greater factor of safety.

Case Reports. Case 1.—W. K., a 36-year-old married woman, referred to us by Dr. John Ruddock, had a typical history of narcolepsy beginning after an attack of influenza 11 years ago. There was no history of encephalitis or head injury. Physical and neurologic examinations were non-contributory. Basal metabolic rate determinations during the course of the past 11 years fluctuated from −18% to 0%. Thyroxin had been tried therapeutically without success. Dosages of 3/8 and ¼ gr. of ephedrine had been tried 3 years ago, which caused faintness and pounding of the heart. Without any medication, she has as many as 4 to 6 sleep attacks a day and a like number of attacks of cataplexy. The effects of the compounds tested are given in Table 3.

Case 2.—P. L., a 34-year-old married Mexican woman, referred to us by Dr. Eugene Ziskind, has had narcolepsy and cataplexy since the age of 13. The attacks of sleep are worse during her menstrual periods and after her meals. She has an average of 4 to 5 sleep attacks and 1 to 2 cataplectic attacks a day. There was no history of head injury or encephalitis. Other than obesity, the general physical and neurologic examination was non-contributory.

This patient was initially given 15, 15 and 10 mg. per day of racemic amphetamine sulphate, which reduced her sleep attacks to 4 per week. Following this, she was given 10, 10 and 6 mg. daily of the dextro-isomer, and she fell asleep but once in the week. The following week a daily dosage

of 20, 20 and 12 mg. of the racemic compound was taken, and she fell asleep but once. After a 2-month interval, a second set of comparisons were made, in which she had 1 sleep attack on 15, 15 and 10 mg. daily of the dextro-isomer, while on 20, 20 and 12 mg. daily of the racemic compound she had 8 sleep attacks.

TABLE 3.—EFFECT OF AMPHETAMINE ISOMERS ON ATTACKS OF SLEEP AND CATAPLEXY OF CASE 1.

	Amphetamine isomer.	Daily doses (mg.).	Attacks in week. Sleep.	Cataplexy.	Sleep at night.
10/22–10/28	Racemic	15, 15, 5	3	0	O.K.
10/29–11/4	Dextro	10, 10, 3	1	0	O.K.
11/5–11/11	Racemic	15, 15, 5	7	4	O.K.
11/26–12/2	Levo	30, 30, 10	4	0	O.K.
12/3–12/9	Dextro	12, 12, 4	2	0	O.K.
12/10–12/16	Racemic	20, 20, 6	4	1	Light
12/24–12/30	Dextro	12, 12, 4	4	3	O.K.
12/31–1/6	Racemic	20, 20, 6	2	0	O.K.
1/7–1/13	Dextro	15, 15, 5	0	0	Poor
1/14–1/20	Levo	30, 30, 10	2	0	O.K.
1/28–2/3	Racemic	20, 20, 6	2	0	Poor

CASE 3.—D. M., a 22-year-old single man, referred to us by Dr. S. J. Sperling, has had a typical history of narcolepsy of 6 years' duration, with occasional attacks of cataplexy. He has been unable to retain any job because of frequent sleep attacks which occurred 4 to 6 times daily. There was no history of head injury or encephalitis. The general physical and neurologic examination was non-contributory.

CASE 4.—F. B., a 30-year-old single woman, referred to us by Dr. Eugene Ziskind, had encephalitis 16½ years ago. Since this time she has had frequent daily attacks of sleep and irritability. She has never had any symptoms of Parkinson's disease nor has she had cataplectic attacks. She had no tremor, rigidity or oculogyric crises. The basal metabolic rate was +3%. Physical and neurologic examinations were non-contributory.

CASE 5.—D. M., a 27-year-old married colored woman, referred to us by Dr. Paul Fitzgibbon, has had narcolepsy as long as she can remember. The condition has become worse during the last 6 or 7 years and at present she falls to sleep 3 to 4 times daily, and suffers from cataplexy during excitement. During one pregnancy the condition was worse. Physical and neurologic examination was essentially negative.

CASE 6.—A 25-year-old single Mexican man, referred by Dr. Paul Fitzgibbon, has had narcolepsy for at least 10 years. He has received several head injuries. In his youth he was kicked by a colt and fell from a horse. He generally has 1 to 3 sleep attacks daily and occasional attacks of cataplexy. Physical and neurologic examinations were non-contributory.

CASE 7.—R. B., a 31-year-old single man, referred to us by Dr. Eugene Ziskind, has had typical postencephalitic Parkinson's disease for 3 years. Without medication, he exhibits marked drowsiness, rigidity and tremor, and usually has several attacks of oculogyric crises daily. Other than the rigidity and tremor, his physical and neurologic examination was negative.

The method of study in this patient was to present him with two bottles of solutions to be used on alternate days during the week. The volumetric dosage was kept constant, but the concentrations and contained compound were varied, and the patient kept a daily record of sleepiness, oculogyric crises, and subjective estimations of energy. Comparison of 20 mg.

dosages of the dextro- and racemic amphetamine sulphates showed the dextro-isomer to be clearly the most active. In comparison with 20 mg. of the dextro-isomer, 30 mg. of racemic amphetamine was less effective and 40 mg. was more effective. The effects of 25 mg. daily of the dextro-isomer was matched by 40 mg. of the racemic compound, or by 50 mg. of the levo-isomer.

CASE 8.—B. S., a 54-year-old married man, referred to us by Dr. Ben Newman, has had typical Parkinson's disease for 1½ years. Although there was no history of encephalitis or influenza, it was believed that the patient probably had the postencephalitic type of the disease because of the therapeutic response to central nervous system stimulating drugs, because the patient's son developed Parkinsonism at the same time, and because of frequent oculogyric crises. Other than the typical mask-like face, tremor, and rigidity, the physical and neurologic examination was essentially non-contributory.

The same method of comparison of the dextro- and the racemic compounds was used as in the above case. It was found that 25 mg. of dextro-amphetamine had a more powerful central stimulatory action than 40 mg. of the racemic compound. The patient was unable to distinguish a difference between the central nervous system stimulating effects of 20 mg. of the dextro- and 40 mg. of the racemic amphetamine.

CASE 9.—R. G., a 34-year-old single man, referred to us by Dr. A. M. Hoffman, had noticed attacks of weakness, dizziness and occasionally syncope for the past few weeks. The symptoms usually occurred when the patient changed from the supine to the upright position. Physical and neurologic examination was essentially negative except that his blood pressure dropped from 120/80 mm. to 70/50 mm. on changing from the recumbent to the upright position.

With this patient it was found that a daily morning dosage of 10 mg. of racemic amphetamine sulphate prevented the attacks of dizziness and weakness without any disturbance of normal sleeping habits. A dosage of 15 mg. of the racemic compound was not notably superior, so the effects of 10 mg. was made the basis of comparison. Daily dosages of 5 and of 6 mg. of the dextro-isomer, or 20 mg. of the levo-isomer, produced comparable effects.

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INFLUENZAL MENINGITIS TREATED WITH SULFAPYRIDINE.

BILATERAL URETERAL OBSTRUCTION, UREMIA, RECOVERY.

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THE discovery of a new drug is apt to be followed by the publication of reports of successes, failures and side-effects observed in patients to whom the drug has been administered. This has been true to an unusual degree in the case of the sulfonamide derivatives. Although we hesitate to add to the flood of literature which has followed in the wake of the discovery of sulfapyridine, yet we believe that the case herewith described is of sufficient importance to warrant our reporting it.

Case Report. A white female, aged 13, had been deaf since she recovered from an attack of cerebrospinal meningitis at the age of 7. A year later she developed an attack of frequent painful urination accompanied by right lumbar pain; a urinalysis at this time was negative and she apparently recovered completely. Two weeks before her present admission, she complained of earache and appeared feverish, but was able to return to school on the following day and had no further complaints until 2 days before admission when she contracted what appeared to her mother to be grippe. On the following day she went to school, but began to feel chilly, developed headache and vomiting and was put to bed. Vomiting continued, and on the following day, February 7, 1940, her neck became stiff and painful and she was admitted to the Episcopal Hospital.

Examination revealed a well-developed, extremely ill and restless girl with flushed cheeks and herpes labialis. The temperature was 104.3°F. The pulse and respiration rates were 132 and 20 respectively. She soon became irrational and her neck more rigid. The rest of the examination was negative; Kernig's and Brudzinski's signs could not be elicited. There were no petechiæ. Lumbar puncture yielded turbid fluid under 19 mm. of mercury pressure containing 6050 cells per c.mm., all of them neutrophils. The protein content of the fluid was increased (+4) and the sugar was 50 mg. per 100 cc. By direct smear, a pleomorphic Gram-negative bacillus was revealed which on culture was identified by Dr. W. P. Belk as *Hemophilus influenzæ* (Pfeiffer's bacillus). A blood culture yielded the same organism. The blood count revealed 31,000 leukocytes, 96% of which were polymorphonuclears and the rest lymphocytes. The urine was negative.

Four hours after admission, she was given 2 gm. (30 gr.) each of sulfapyridine and sodium bicarbonate, and thereafter 1 gm. of each of these drugs every 4 hours night and day. A second lumbar puncture on the following day yielded fluid under 14 mm. Hg pressure with 3648 cells per cubic millimeter, 38% of which were neutrophils and 12% lymphocytes.

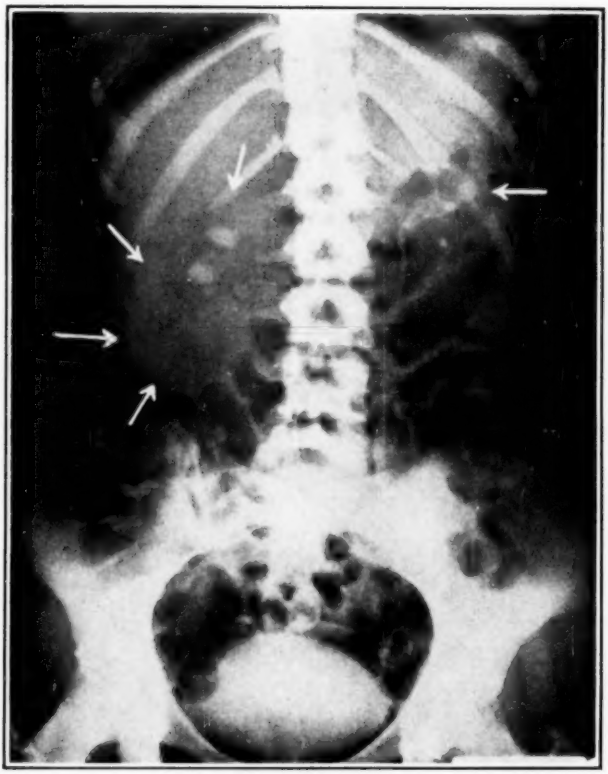

FIG. 1.—Partial recovery. Urogram 12 days after complete bilateral ureteral obstruction from sulfapyridine therapy. Shows slight excretion of dye from swollen right kidney. Left kidney has apparently returned to normal.

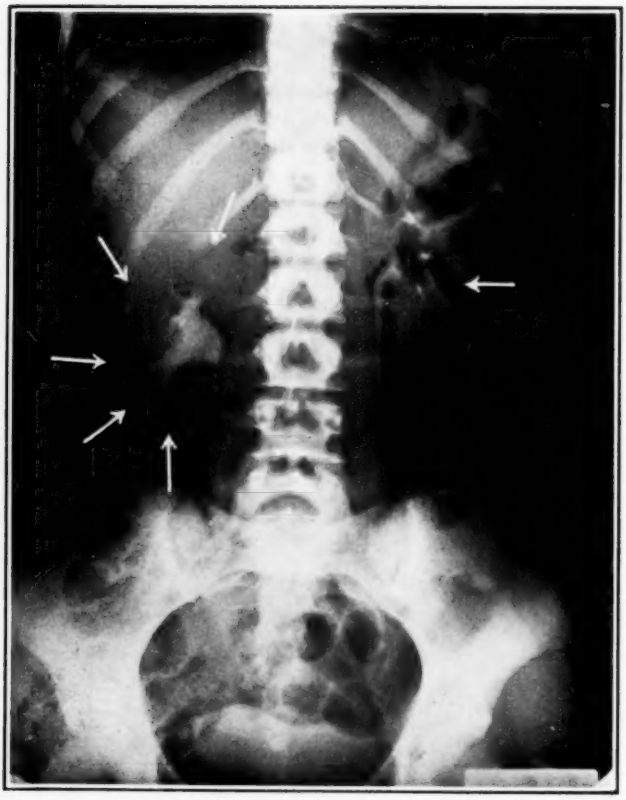

FIG. 2.—Urogram 12 days later, showing good concentration and excretion by both kidneys, with moderate hydronephrosis and clubbing of some of the calyces of the right, probably due to previously existing ptosis.

The protein was increased (+1) and *Hemophilus influenzæ* was again secured by culture, though no organisms were seen in the direct smear. Two days later her temperature had dropped to normal, the spinal fluid was sterile and contained only 90 cells, and the blood culture was sterile. In spite of the dramatic response to sulfapyridine therapy, fearing the possibility of a relapse, the drug was continued in full dosage, until, on February 17, having received 47 gm. of sulfapyridine, she vomited and complained of pain in the right flank. Abdominal examination revealed a tense, tender, freely palpable mass corresponding to the right kidney. The ease with which this mass was felt indicated a marked renal ptosis. With the hope of relieving a possible obstruction of the right ureter, cystoscopy was promptly undertaken.

Cystoscopy. The tolerance and capacity of the bladder appeared normal. Lying on the bladder floor was seen considerable putty-like débris streaked with blood. With close observation this material presented a golden sandy appearance. Extruding from the left ureteral orifice was seen a blood clot. Active peristalsis of both ureteral orifices was noted, and there was an occasional sluggish ejection of bloody urine from the left. No urine appeared from the right orifice during the examination. There was no evidence of indigo carmine from either side in 15 minutes. Attempts to catheterize the right ureter revealed a complete block at the 2.5-cm. level, and this obstruction could not be passed. A No. 4 ureteral catheter was passed with some difficulty to the 22-cm. level up the left ureter. There was free drainage of bloody urine through the catheter. This catheter was unfortunately withdrawn with the optimistic thought that the left ureter would remain patulous.

During the next 24 hours she was completely anuric. The blood urea nitrogen, which on admission had been normal, rose to 55, and a generalized convulsion lasting for 2 minutes occurred. The blood pressure was 105 over 78, the temperature 100° F., and the pulse and respiratory rates 92 and 18 respectively.

Because of these developments ureteral catheterization was again attempted. On passage of the cystoscope, approximately 8 cc. of very bloody urine was drained from the bladder. The putty-like débris of the first examination was again noted. A No. 5 ureteral catheter was passed to the 6-cm. level up the left ureter and met an obstruction at this point. With the catheter at this level, hot sterile distilled water was gently forced through the catheter but without effect. The catheter was withdrawn and after manipulation a No. 7 ureteral bougie was finally passed to the left renal pelvis. Upon withdrawal of this a No. 5 ureteral catheter was passed to the left renal pelvis, which resulted in a free drainage of urine. The catheter was left *in situ*. Attempts to relieve the right ureteral obstruction were again unsuccessful. During the next 24 hours 950 cc. of alkaline urine of low specific gravity containing abundant albumin and erythrocytes and leukocytes was passed through the catheter.

During the next 15 days the patient had fever ranging from 99° to 104° F., but the urinary output was satisfactory. On February 20 the ureteral catheter was removed. The urine passed immediately thereafter was very cloudy, containing shreds, débris, many pus cells and frequently erythrocytes.

On February 29 an intravenous urogram (Fig. 1) showed a normal left urinary tract, while the 30-minute film on the right revealed faint evidence of the dye with marked hydronephrosis and ptosis.

On March 12, following steady improvement, a second intravenous urogram (Fig. 2) revealed good concentration on both sides, the left tract being normal. The right showed moderate dilatation of the renal pelvis and early clubbing of the minor calices, presumably due to preëxisting ptosis.

The patient was discharged on March 15 in good condition. Examination in the "Follow-up Clinic" on April 19 revealed no symptoms and the patient in good health.

Comment. A search of the literature of 1938 and 1939 has revealed seven reports[3,9,12,13,15,16,22] concerning the use of sulfapyridine in the treatment of 25 cases of meningitis due to *Hemophilus influenzæ*, with 14 recoveries.* This mortality of 44% is in marked contrast with the mortality of 82% and 98% respectively in cases treated with and without specific serum.[7] Sulfanilamide, too, has been used with and without serum,[5,6,11,17,19,20,22,23] but the results are not as impressive as with sulfapyridine.

Ureteral obstruction is a well-recognized complication[2,4,10,21] of sulfapyridine therapy. From animal experimentation[1,8] and clinical observation[14,18] it has been learned that acetylated sulfapyridine crystals frequently are excreted by animals and human beings receiving the drug. In most cases they are no doubt harmless, but when present in excess they may irritate or obstruct the collecting tubules or upper urinary tract, leading to hematuria or anuria, largely if not wholly mechanical in origin. The blood clots themselves, no doubt, may be a factor in the production of obstruction; in our case a mixture of blood clots and crystals could be seen obstructing the left ureter. The fact that the conglomerate mass could not be dislodged by ureteral lavage with warm water is not surprising since acetylated sulfapyridine crystals are poorly soluble in water and are probably rendered more insoluble by the admixture of coagulated blood. Only by manipulation of the ureteral bougie could the obstruction in the left ureter be passed, permitting the subsequent insertion of a ureteral catheter. The obstruction in the right ureter later disappeared spontaneously. Perhaps the obstruction in the left would similarly have disappeared had we been willing to withold cystoscopic manipulation at the risk of death from anuria. In any case, our experience would lead us to believe that where the life of the patient is not seriously threatened, conservative measures (high fluid intake without cystoscopic manipulation) should be given adequate trial. The terms, uroliths and concretions, hardly describe accurately the putty-like appearance of the masses of crystals when seen cystoscopically. Although apparently too insoluble to be dislodged by lavage while on the table, the fact that they spontaneously dissolved and were painlessly passed in the form of sediment in the space of a few days is in marked contrast with the behavior of ordinary uroliths or concretions.

Summary. The case of a 13-year-old girl is reported who, following sulfapyridine therapy, recovered from influenzal meningitis but

* Two more cases with recovery are being reported by Dr. E. L. Noone. One case of fulminating influenzal encephalo-meningitis with a positive blood culture was treated with sulfapyridine on Dr. James Kay's service in the Episcopal Hospital and died: one case treated with sulfapyridine, serum and sulfathiazole on Dr. Leonard F. Bender's service recovered.

almost succumbed to bilateral ureteral obstruction. This case emphasizes: 1, The value of sulfapyridine in the treatment of influenzal meningitis; 2, its potentialities for damage to the upper urinary tract; and 3, satisfactory recovery after complete ureteral blockage.

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DELIRIUM TREMENS.

A Study of Various Methods of Treatment.*

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In 1937 a report was presented from this clinic by Piker and Cohn[14] on the comprehensive management of delirium tremens. This report was based on a study of 300 consecutive cases of delirium tremens from January 1, 1933, to July 1, 1935. These cases were all submitted to a routine type of therapy and a brief review of the treatment is as follows:

* Read before the American Psychiatric Association, May 23, 1940, in Cincinnati, Ohio.

1. No alcohol is given the patient from the time that he comes under our direction.
2. Absolute bed rest is ordered in an attempt to avoid as far as possible physical strain on the heart, and to give the patient the maximum opportunity for sleep.
3. Close observation on the part of the ward personnel is insisted on, so that the patient has a minimal chance to injure himself or others.
4. Extract of cascara, 10 gr. (0.6 gm.), is given on admission, followed by 1 ounce (30 gm.) of magnesium sulphate by mouth 2 hours later.
5. Magnesium sulphate (1 ounce) is given every morning for 3 days, unless there have been more than 4 bowel movements the previous day.
6. Alkalies in the form of imperial drink (potus imperialis, British Pharmaceutical Codex) are given 3 times daily.
7. Spinal fluid drainage is done as soon after admission as possible, and may be repeated as often as is indicated.
8. Fifty cubic centimeters of 50% dextrose is given intravenously from 2 to 4 times a day.
9. Ten cubic centimeters of 50% magnesium sulphate is given intramuscularly 1 to 2 times a day for 2 days.
10. Caffeine sodium benzoate, 7½ gr. (0.5 gm.), is given hypodermically every 4 hours for 6 doses. If indicated, this procedure may be repeated.
11. The patient is digitalized in from 36 to 48 hours, and is then placed on a maintenance dose.
12. Paraldehyde (100%), 3 or 4 drams (from 11 to 15 cc.), is given from 1 to 3 times a day for sedation. Intravenous sodium amytal may be used, though we would hesitate to recommend that more than from 10 to 15 gr. (0.6 to 1 gm.) be given to any one patient. Hydrotherapy is indicated wherever possible.
13. A high caloric soft or liquid diet, supplemented by vitamin-containing substances—especially of the B group—is ordered. If the patient has difficulty in retaining nourishment, gastric lavage with a sodium bicarbonate solution should be done.
14. Fluids are given according to the patient's desires. The factor of the patient's comfort should be the determining one in governing the amount of fluids given.
15. Should the patient be asleep, he is not awakened for any reason, medicinal or otherwise.

Under this régime the mortality rate was 5.3% and the average stay in the hospital was 4.8 days.

The purpose of this paper is to review the results of treatment in 234 consecutive cases of delirium tremens admitted to the Psychiatric Pavilion of the Cincinnati General Hospital from July 1, 1935, to February 1, 1940. Cases in this group all showed the characteristic findings of delirium tremens, that is, a history of alcoholism with an acute psychosis characterized by disorientation, hallucinations, apprehension, tremors, insomnia, anorexia, and general signs of toxicity. Although cases of so-called "incipient delirium tremens" (same as delirium tremens with absence of psychotic manifestations) are treated in our clinic similarly to the full-blown delirium tremens cases, none of these are included in this study. Since the original report in 1937, we have instituted changes in treatment which will be discussed in this and subsequent reports.

Modifications in Treatment and Their Results. In order to evaluate the efficacy of various treatment maneuvers we have arbitrarily chosen as our basis of comparison three factors common to all cases.

1. The duration of psychotic material. We considered a patient no longer psychotic when he became oriented, stopped hallucinating, and was devoid of delusions.

2. The length of hospital stay. This was determined by complete recovery from the disease. In addition to absence of psychotic material, we used as criteria for recovery the absence or marked diminution of tremors, return of appetite, ability to sleep satisfactorily, and loss of apprehensiveness.

3. The amount of paraldehyde used in each case. We interpreted this factor as an index of the turbulency of the patient's course.

Since there were only 3 deaths in this series, we did not include the mortality rate as a factor in judging the various treatments used.

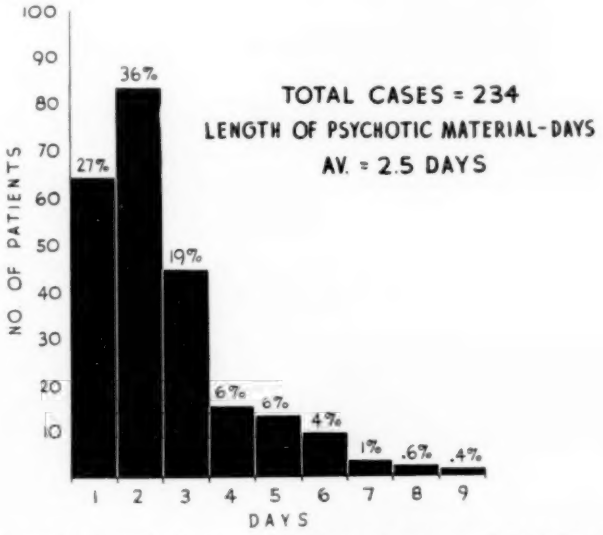

FIG. 1.—Length of psychotic material in days of 234 cases of delirium tremens regardless of type of therapy.

Figures 1 and 2 illustrate the duration of psychotic material and duration of the disease respectively for the total group of 234 cases, regardless of variations in treatment and calculated from time of admission to the hospital. The average duration of psychotic material was 2.5 days, and the average duration of the disease (hospital stay) was 5.3 days.

Fluids. One of the first modifications in the treatment routine was forcing fluids. Since this subject has already been discussed by Piker,[13] we will only present his conclusions.

Figure 3 illustrates the results in 142 cases treated with routine therapy and forced fluids (3000 to 4000 cc. daily). The average duration of illness was 4.75 days; while in a similar group of 142 cases in whom fluids were limited (under 1000 cc. daily), the average duration of illness was 4.65 days. The mortality rate was the same—8 deaths in each series.

Digitalis. The second modification in the treatment was the omission of digitalis. In Figure 4 it is seen that in a group of 91 cases treated with routine therapy plus digitalis, the average duration of psychotic material

was 2.1 days, as compared to 2.3 days in a group of 59 cases treated without digitalis. The average hospital stay in the digitalized group was 4.8 days, as compared to 5 days in the non-digitalized group. The average paraldehyde was 16 drams, as compared to 18 drams.

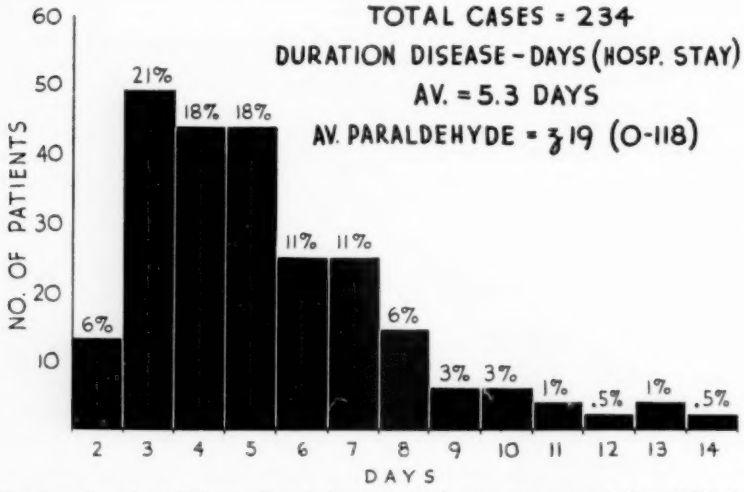

FIG. 2.—Duration of disease (hospital stay) and the average amount of paraldehyde used in 234 cases of delirium tremens regardless of type of therapy.

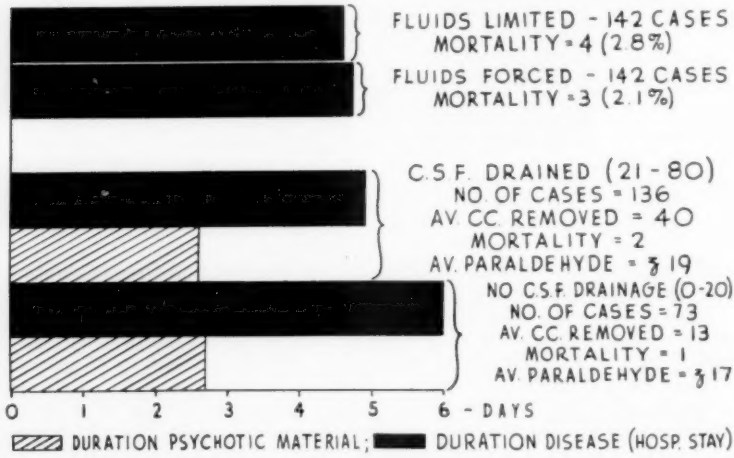
FLUIDS LIMITED - 142 CASES
MORTALITY = 4 (2.8%)
FLUIDS FORCED - 142 CASES
MORTALITY = 3 (2.1%)
C.S.F. DRAINED (21 - 80)
NO. OF CASES = 136
AV. CC. REMOVED = 40
MORTALITY = 2
AV. PARALDEHYDE = ʒ 19
NO C.S.F. DRAINAGE (0-20)
NO. OF CASES = 73
AV. CC. REMOVED = 13
MORTALITY = 1
AV. PARALDEHYDE = ʒ 17
0 1 2 3 4 5 6 - DAYS
DURATION PSYCHOTIC MATERIAL; DURATION DISEASE (HOSP. STAY)

FIG. 3.—Results in 284 cases of delirium tremens treated with routine therapy in which fluids were limited (under 1000 cc.) in 142 cases (Piker and Cohn). (A comparison of results in 136 patients who had cerebrospinal fluid drainage with 73 patients who were not drained of cerebrospinal fluid. Note similarity in results in all groups.)

Sucrose and Glucose. The next change in treatment was the substitution of sucrose for glucose. In Figure 4 it is seen that in 86 patients treated with

routine plus glucose (the majority of these patients were digitalized), the average psychotic duration was 2.6 days as opposed to 2.5 days in 107 patients treated with routine plus sucrose (the majority of these patients were not digitalized). The average hospital stay was 5.3 days in the glucose group, as compared to 5.7 days in the sucrose group; and the average paraldehyde was 15 drams, as compared to 20 drams.

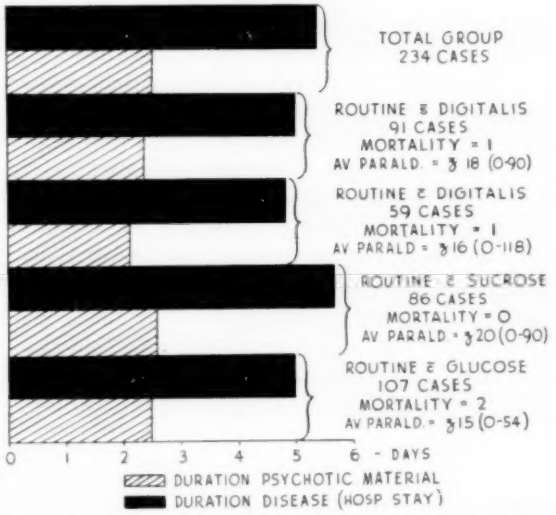

FIG. 4.—Comparison of results in patients treated with and without digitalis. (Results in patients treated with intravenous sucrose [50 cc. of 50% solution b.i.d.] as compared to patients treated with glucose [50 cc. of 50% solution b.i.d.]. Note similarity in results in all groups.)

Cerebrospinal Fluid Drainage. Figure 3 compares results in 136 cases in which more than 21 cc. of spinal fluid was drained at one tap, to 73 cases in which less than 21 cc. was drained. The average amount drained from the first group was 40 cc.; and the average drainage from the second group was 13 cc. The average psychotic duration for the two groups was 2.6 days and 2.7 days, the average hospital stay 5.2 days and 6 days, and the average paraldehyde used 19 drams and 17 drams.

Vitamins. In 1936 we treated 17 cases with liver extract parenterally. In Figure 5 it is seen that the average psychotic duration in these cases was 3.3 days, the average hospital stay 5.3 days, and the average paraldehyde was 18 drams. The introduction of refined vitamin preparations such as thiamin chloride (B_1) and nicotinic acid led us to try these preparations. In June, 1938, we started to use nicotinic acid orally (500 to 1500 mg. daily) in addition to routine treatment; and Figure 5 illustrates the results in a group of 14 cases. The average psychotic duration was 3.2 days, the length of illness was 7 days and average paraldehyde was 38.5 drams.

In July, 1939, we began to treat alternate cases of delirium tremens with vitamin B_1* (50 mg. daily, parenterally), paraldehyde, and a diagnostic lumbar puncture. Figure 5 illustrates the results. The average psychotic duration of the B_1 group was 2.2 days, as compared to 2 days in the control

* Vitamin B_1 supplied through the courtesy of the Wm. S. Merrell Chemical Company, Cincinnati, Ohio.

group; the hospital stays were 6.6 days and 5.5 days; and the average amounts of paraldehyde used were 11.3 drams and 15 drams.

Miscellaneous. In addition to the above we have a small number of cases given sodium chloride with the routine treatment, and 4 cases treated only with insulin covered by glucose. These groups are too small for evaluation; but an interesting fact is that 3 of the 4 insulin-treated cases required no sedation.

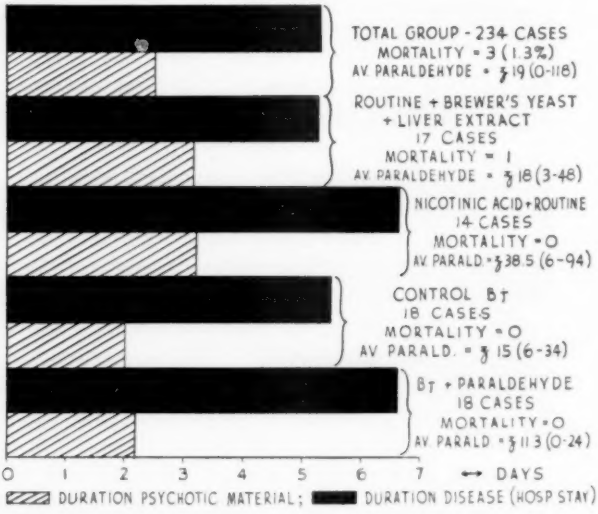
TOTAL GROUP - 234 CASES
MORTALITY = 3 (1.3%)
AV. PARALDEHYDE = ʒ 19 (0-118)
ROUTINE + BREWER'S YEAST
+ LIVER EXTRACT
17 CASES
MORTALITY = 1
AV. PARALDEHYDE = ʒ 18 (3-48)
NICOTINIC ACID + ROUTINE
14 CASES
MORTALITY = 0
AV. PARALD. = ʒ 38.5 (6-94)
CONTROL B1
18 CASES
MORTALITY = 0
AV. PARALD. = ʒ 15 (6-34)
B1 + PARALDEHYDE
18 CASES
MORTALITY = 0
AV. PARALD. = ʒ 11.3 (0-24)
0 1 2 3 4 5 6 7 DAYS
DURATION PSYCHOTIC MATERIAL; DURATION DISEASE (HOSP STAY)

FIG. 5.—The use of vitamins in treatment of delirium tremens. (Note the similarity in results of the 18 patients treated with B_1 to the 18 controls [routine treatment without vitamins]. Also the increase in duration of psychotic material and hospital stay in the nicotinic acid group.)

Discussion. We would agree with Bowman[1] and his workers that although a good deal is known about delirium tremens from the clinical aspect, little is known as to the exact etiology. We emphasize that our treatment is purely symptomatic, except in those cases treated with only vitamin B_1 and paraldehyde in an attempt to evaluate the factor of B_1 deficiency.

Fluids. Piker[13] has already shown that there was no difference in the outcome of his cases regardless of whether fluids were forced or limited. Originally we limited fluids to counteract the cerebral edema and the supposed increased intracranial pressure in these cases; but since it has been felt that the general toxic factors were more important, we have been forcing fluids as part of our routine.

Digitalis. In our series, there is not much difference in results in patients treated with or without digitalis. The drug was originally used to prevent cardiac failure, as it was noted that most cases coming to autopsy have two characteristic diagnoses: cerebral edema ("wet brain") and toxic myocarditis with acute dilatation. It was thought that the drug might prevent the latter. However,

we no longer use digitalis in our treatment, because as already noted, patients recover as quickly without it as with it; and inasmuch as delirium tremens in itself involves considerable toxicity, it appears rational to eliminate any toxic drug such as digitalis. There is a general agreement among cardiologists and internists that digitalis is probably contraindicated in toxic states of all sorts.[4,17] Furthermore, we have noted no decrease in the tachycardia of this disease with digitalis.

Sucrose and Glucose. In 1934 and after there were reports in the literature[2,3,7,8,11] to the effect that sucrose was a better agent for reducing intracranial pressure than glucose. Sucrose tended to keep the pressure down for longer periods, and prevented the development of a late rise in cerebrospinal fluid pressure. Since one aim of our therapy was to reduce increased intracranial pressure and cerebral edema, we started to use sucrose intravenously (50 cc. of a 50% solution B.I.D.).

At this point it may be appropriate to say a few words about this subject of cerebral edema ("wet brain") and increased cerebrospinal fluid pressure in delirium tremens. There has been a good deal of speculation about cerebral edema and increased cerebrospinal fluid pressure in this disease mainly due to one fact: that in patients dying with delirium tremens the most consistent cerebral finding is that of cerebral edema. To our knowledge, no conclusive work has been done on this subject, although it has been shown by Rosenbaum, Herren, and Merritt[16] that only 25% of acute alcoholics (including delirium tremens cases) have increased intracranial pressure (180 mm. and above), and it has also been noted by Rosenbaum and Merritt[15] that in 38 cases of acute Korsakoff psychosis, only 16% show increased pressure (180 mm. and above). About 25% of our cases showed increased pressure (180 mm. and above). (This subject will be discussed in detail in another report.)

It suffices to say at the present that although it appears that the majority of patients with delirium tremens have normal pressure, there is no proven causal relationship between cerebral edema and cerebrospinal fluid pressure. Therefore, we used sucrose and glucose to combat cerebral edema even in the face of normal cerebrospinal fluid pressure. Our results show little difference insofar as the two solutions are concerned. It is likely, however, that carbohydrate metabolism is disturbed in this disease; and attempts should be made to correct this. Sucrose injected intravenously is not utilized in carbohydrate metabolism.[2,3,7,8,11] Moreover, it is established that a high percentage of glucose injected intravenously in strongly hypertonic solutions is excreted in the urine,[18] with only a small fraction being utilized in carbohydrate metabolism. Consequently, we believe that the most rational approach to this problem would be the administration of hypertonic sucrose to combat cerebral edema (and increased cerebrospinal fluid pressure when

present), and the use of carbohydrates by mouth, or in 5% to 10% solution by slow intravenous injection if the oral route is not feasible.

Cerebrospinal Fluid Drainage. Until about a year ago most patients were drained of spinal fluid in an attempt to alleviate cerebral edema. In the past year only diagnostic taps were done. Since there were only 28 cases who had less than 10 cc. taken off at one tap, we included 45 cases from whom between 11 and 20 cc. had been drained to make a total of 73 cases in what we considered the "non-drainage" group. As already noted, there is no difference in results in these groups. At present, our policy is to reduce the pressure by half if increased; and if not increased, to remove enough for routine spinal fluid examination.

Nutrition. In the last several years the whole concept of alcoholism, especially regarding pathologic effects on the nervous system, has been subject to a new point of view, namely the rôle of vitamin deficiency in these cases. It has long been known that the alcoholic eats little; or, if he eats, that he utilizes inadequate amounts of the ingested food. Spies and De Wolf,[19] Strauss,[21] Wechsler,[22] Goodhart and Jolliffe,[6] and many others have suggested that the main effect of alcohol on the nervous system was not caused by the alcohol itself, but by the vitamin deficiency connected with the alcoholism. Most of this work has been done on so-called alcoholic peripheral neuritis. Inasmuch as the alcoholic who develops delirium tremens is a notoriously poor eater, and furthermore usually shows gastro-intestinal symptoms before and during delirium tremens, we felt we should attack this deficiency by the addition of vitamins of the B group.

Only 17 cases were treated with liver extract (10 cc., deep injection daily). These patients did no better than the routine group; and as a matter of fact had a longer duration of psychotic material, namely 3.3 days.

We first used nicotinic acid in addition to our routine therapy in June, 1938, after it had been shown by Spies and his workers[20] that this vitamin was specific in the acute psychosis of pellagra. Maizner and Krause[10] reported the use of nicotinic acid with good results in 1 case of delirium tremens. The 14 cases we treated with nicotinic acid had an average psychotic duration of 3.2 days, which is almost a day longer than the group treated without any vitamin; and they also required an average of 38.5 drams of paraldehyde, which is about twice as much as the non-vitaminized group needed. This seems to suggest that the addition of nicotinic acid prolongs the illness, if it does anything. As already stated, one aim in treatment is to relieve cerebral edema and increased cerebrospinal fluid pressure when present. Moore[12] has shown that nicotinic acid causes dilation of the cerebral blood-vessels; and it has also been demonstrated by Ferris, Rosenbaum, Roseman, and Brower[5] that nicotinic acid increases the rate of cerebral circulation and raises

intracranial pressure. It is perhaps these factors which tend to aggravate and make for cerebral edema that account for the increase in duration of psychotic material in these patients. We believe that nicotinic acid is not warranted in treatment unless a specific nicotinic acid deficiency exists in the patient.

Recently there has been a great deal of interest in the use of thiamin chloride (vitamin B_1) in all sorts of psychiatric, neurologic, and medical conditions. There have been several reports of its use in delirium tremens, mainly in the foreign literature. Kloster[9] treated 10 patients with this drug; and though he realized this was too small a group for true evaluation, he did notice that the patients slept well with the drug. Since July, 1939, we have treated alternate cases with B_1 (50 mg. daily) and paraldehyde; and although this work is still in progress, we feel justified in making a preliminary report of 18 cases, with 18 controls treated routinely. As was noted earlier there was not much difference in the course of the two groups, except the group treated with B_1 required not only less paraldehyde than the controls, but less than any other group in our entire series. This finding is consistent with the supposed sedative action of B_1. Two patients in this group required no paraldehyde at all. However, what is more interesting and striking is that 2 patients came in with incipient delirium tremens, received B_1 (50 mg. daily) from the time of admission, and developed typical delirium tremens after being in the hospital 2 days. These observations lead to the question of whether a B_1 or nicotinic acid deficiency plays any part in the production of this syndrome. From our experience so far all we can conclude is that once the disease starts, the addition of B_1, nicotinic acid, liver extract, and Brewer's yeast do not seem to aid in shortening the illness. This brings up the following question: Is the vitamin or nutritional deficiency an important precipitating factor, even though vitamin treatment does not influence the illness once it starts? One way to approach this problem would be to allow an alcoholic to drink all he wants, but to make certain his vitamin intake during his drinking period has been adequate, that is, along the lines adopted by Spies and De Wolf[19] and Strauss[21] in their study of alcoholic pellagra and alcoholic neuritis.

TABLE 1.—SUMMARY OF THE ROUTINE TREATMENT OF DELIRIUM TREMENS FROM PIKER AND COHN.

Principles.	*Methods.*
Safeguarding the patient	Hospitalization Adequate observation
Prevention of exhaustion	Circulatory support (digitalis, caffeine, glucose) Sedation (paraldehyde, spinal fluid drainage, caffeine, glucose, $MgSO_4$)
Promotion of elimination	Bowel (cascara, $MgSO_4$) Kidney (caffeine, glucose, digitalis)
Decrease of cerebral edema	Spinal fluid drainage Glucose, $MgSO_4$, caffeine
Promotion of nutrition	Readily digestible, high calorie, high vitamin diet For severe gastritis, lavage

We have attempted to answer the question by doing just this, and at this time would like to mention the experiment. A chronic alcoholic who was admitted to the Psychiatric Service four times during the past year with delirium tremens volunteered for the study after fully recovering from his last episode. He consumed 12½ quarts of whiskey (90 proof) in 14 days; and each day he received 50 mg. B_1 (parenterally) and 500 mg. nicotinic acid (orally). He ate practically nothing during the experiment, although he consumed large quantities of milk daily, using it as a chaser. On the thirteenth day of his drinking he developed delirium tremens. We realize that this is only 1 case; but it seems safe to assume that in this 1 case the delirium tremens was not on the basis of a B_1 or nicotinic acid deficiency.

TABLE 2.—ANALYSIS OF MORTALITY FIGURES IN 534 CASES OF DELIRIUM TREMENS.

Mortality Figures.	
July 1, 1935 to February 1, 1940:	
234 cases—Total deaths	3 (1.3%)
Uncomplicated deaths	2 (0.9%)
Severe Complications.	
Lobular pneumonia and acute renal insufficiency	1
January 1, 1933 to July 1, 1935:	
300 cases—Total deaths	16 (5.3%)
Uncomplicated deaths	7 (2.3%)
9 severe complications:	
Suppurative parotitis and bronchopneumonia	1
Severe gastric hemorrhage and lobar pneumonia	1
Heat stroke	2
Lobar pneumonia	3
Severe bronchopneumonia	1
Severe stab wounds of chest and abdomen	1
Combined mortality, 534 cases:	
Total deaths	3.5%
Uncomplicated deaths	1.7%

Deaths (Table 2). Though the number of deaths in our series was too small to permit the use of mortality figures as an index of the comparative values of the treatment variations we have discussed, it would be well to review these figures. In the 234 cases with which this paper is chiefly concerned, there were 3 deaths, a mortality rate of 1.3%. Comparing this rate with the one of 5.3% reported by Piker and Cohn from this clinic would seem to present an appreciable discrepancy. The explanation for this discrepancy is as follows: previous to July 1, 1935, all patients with delirium tremens (regardless of type or severity of coincidental complicating disease) were treated on the Psychiatric Service. As a result, the 16 deaths occurring in the series of 300 cases reported by Piker and Cohn included 9 whose conditions were primarily medical or surgical, whose delirium tremens was secondary, and whose deaths should most properly be ascribed to changes not associated with delirium tremens. These 9 cases included 1 suppurative parotitis and bronchopneumonia, 1 severe gastric hemorrhage and lobar pneu-

monia, 2 heat strokes, 3 lobar pneumonias, 1 severe bronchopneumonia, and 1 case of severe stab wounds of the chest and abdomen. If these cases are deleted from the series, the mortality rate becomes 2.4%. Similarly, the 3 deaths in the more recent group included 1 patient who had severe lobular pneumonia, and who was transferred to the Medical Service and died there. With this case omitted, the mortality rate for the more recent series becomes 0.9%.

Combining the two groups, and including only those patients who had either complications of secondary importance or none at all, the mortality rate for 524 consecutive cases of delirium tremens treated variously in our clinic becomes 1.7%.

Conclusions. A total series of 524 consecutive cases of delirium tremens was treated in the Psychiatric Division of the Cincinnati General Hospital from January 1, 1933, to February 1, 1940. Several different treatment maneuvers were attempted with several subgroups of this series, with the variation in results being for the most part insignificant.

The similarity in results, regardless of type of therapy used, suggests that the treatments be examined for factors common to all of them. Insofar as we have been able to discover, these common factors included only hospitalization, paraldehyde, lumbar puncture (some for drainage and some for diagnostic purposes), and the attitude toward these patients on the part of the department personnel. Of these factors, our attitude seems to us perhaps particularly significant. Delirium tremens has been for several years the chief research problem of the department. As a result much time is given to delirium tremens patients, with the interest of the research clinicians permeating everyone involved in the management of these cases. The *esprit de corp* that has developed in this connection is apparent in the general reaction of personal defeat on the part of the entire personnel when 1 of these patients dies.

A consideration of this attitude has led us to speculate regarding the value of "superficial" psychotherapy (much attention, reassurance, and our own feeling of confidence growing out of our low mortality rate) in delirium tremens. It is of interest in this regard that numerous repeaters return to our wards of their own accord when they begin to feel "jittery." Furthermore, we find it difficult to ignore the fact that 2 patients relaxed into satisfactory sleep after being given placebos. And finally, our results seem to us to indicate strongly that regardless of what sort of treatment procedure is used, and so long as no measures are instituted which are actually injurious, adequate general medical and psychiatric care should serve to keep the mortality rate in uncomplicated delirium tremens down to a minimum.

We have been unable to find, thus far, a specific therapeutic medicinal procedure for delirium tremens. It is our feeling that

the place of psychotherapy in the treatment of this disease merits more consideration generally than it has received until now.

In the light of our low mortality figures, it seems to us that the problem in delirium tremens at this time is not so much one of discovering the proper method of therapy as it is an elucidation of the etiologic factors involved.

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THE PRODUCTION OF FATTY AND FIBROTIC LIVERS IN GUINEA PIGS AND RABBITS BY SEEMINGLY ADEQUATE DIETS.*

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Fatty livers have been produced in experimental animals in various ways. These methods involve the use of a toxic agent (carbon tetrachloride,[4] chloroform,[8] or phosphorus,[12] surgical extirpation of organs such as pancreatectomy,[3] removal of 65% of liver,[12] or use of a grossly unbalanced diet deficient in protein and overabundant in fat.[1,2,11] In 1939, we[20] reported the production of fatty livers in the guinea pig by means of a diet which appears to be well balanced but devoid of vitamin C. Our work at that stage suggested that the absence of vitamin C was not wholly responsible for this pathologic change. In the present study we have extended

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these observations and investigated the relationship of other substances to this type of experimentally produced liver damage.

Fatty Livers Produced by Scorbutogenic Diet (Table 1). The diet we used was essentially the scorbutogenic diet originated in 1922 by Sherman *et al.*,[18] except that whole milk powder was used instead of skimmed milk powder. This diet we shall refer to as Diet 1 (Table 5). A group of guinea pigs were put on this diet and were given an abundance of ascorbic acid. This was administered by means of a syringe by mouth, as an aqueous solution. This supplement was withdrawn after about 3 weeks and the animals were allowed to die from scurvy. Another group of animals were given subminimal doses of ascorbic acid to prolong their survival (Table 1).

TABLE 1.—EFFECT OF SCORBUTOGENIC DIETS ON LIVER FAT.

Serial No. of animal.	Diet.		Vitamin C.		% liver of body weight.	Mg. lipids per 1 gm. liver tissue.
	Type.	No. of days.	Amount.	No. of days.		
SIM 3	Starved	11	Abund.	..	4.1	13.6
NM 1	Normal	..	Abund.	..	...	21.2
NM 2	Normal	..	Abund.	..	5.3	24.0
NM 3	Normal	..	Abund.	..	...	19.9
IM 1	1	47	Free	25	10.5	238.8
IM 2	1	50	Free	28	9.3	260.9
IM 4	1	49	Free	27	8.0	109.3
IM 5	1	50	Free	28	7.7	117.9
IM 6	1	52	Free	30	6.9	122.1
HM 1	1	54	Low	54	8.6	207.0
HM 2	1	33	Low	33	...	130.7
HF 3	1	53	Low	53	4.7	63.7
HF 4	1	67	Low	67	5.06	91.5
HF 1	1	117	Low	117	6.8	300.6
GM 2	2	46	Free	21	7.5	116.6
GF 3	2	46	Free	21	6.9	104.5
GF 4	2	48	Free	6	6.8	78.5
GM 4	2	49	Free	7	6.6	125.0
GF 5	2	58	Free	17	7.5	110.3
GF 6	2	55	Free	14	6.03	39.1

All animals were autopsied, and organs showing noteworthy gross changes were taken for microscopic examination. Sections of liver tissue were stained by eosin and hematoxylin and Sudan 3. A total of about 0.5 gm. of tissue was taken from the various lobes of the liver to obtain an average sample. This was analyzed for total lipids by the micro-method of Van Slyke.[10] The livers of the animals that were completely deprived of vitamin C showed a lipid content of 10.9% to 26%, while those on the subminimal amounts of vitamin C and dying from chronic scurvy had liver fat content of 6.3% to 30%, depending roughly on the length of time they survived (Table 1).

Effects of Yeast and Dextrose on Liver Fat (Table 1). Since dextrose has been thought to have a favorable effect on various types of liver injury, we modified the above diet by replacing part

of the bran and oats with 10% dextrose. The 1% desiccated brewer's yeast was added to neutralize the loss of the B complex created by the removal of 11% of bran and oats (Table 5) (Diet 2). A group of 6 guinea pigs were put on this diet and allowed to die from scurvy. The livers of these animals contained 3.9% to 12.5% of fat, which is considerably less than the amount present in the livers of animals on Diet 1. This apparently favorable effect of dextrose and yeast is refuted in the following experiment.

Effect of Ascorbic Acid and Orange Juice on Liver Fat (Table 2). Four groups of guinea pigs were used (Table 2). Group 1 was fed on Diet 1 supplemented by an abundance of pure ascorbic acid. Group 2 was also on Diet 1 but received orange juice as the antiscorbutic agent. Groups 3 and 4 were fed Diet 2, supplemented with crystalline ascorbic acid and orange juice respectively.

TABLE 2.—INFLUENCE OF YEAST, ORANGE JUICE, AND CRYSTALLINE ASCORBIC ACID ON LIVER FAT.

Serial No. of animal.	Diet. Type.	Diet. No. of days.	Vitamin C.	% of liver of body weight.	Mg. lipids per 1 gm. liver tissue.
1 EM 2	1	46	Cryst.	7.1	129.2
1 EF 5	1	67	"	7.04	136.6
1 EF 3	1	74	"	8.8	302.4
1 EM 4	1	142	"	7.2	319.2
1 EF 8	1	42	O. J.	4.1	38.3
1 EF 9	1	42	"	7.7	105.1
1 EF 7	1	62	"	7.3	142.3
1 EF 6	1	173	"	...	194.3
EF 2	2	100	Cryst.	4.8	74.8
EM 1	2	154	"	11.3	238.4
2 EM 3	2	34	"	7.3	110.5
2 EM 1	2	58	"	7.1	122.7
2 EM 2	2	92	"	8.99	326.9
2 EF 4	2	157	"	9.3	342.0
2 EM 5	2	63	O. J.	8.5	248.4
2 EM 6	2	341	"	4.5	125.7
2 EM 7	2	217	"	5.9	222.7
2 EM 8	2	213	"	9.3	340.2

It will be noted that the group receiving the orange juice with Diet 1 had a lower liver fat content than those on this diet with the ascorbic acid. Thus the group on the pure ascorbic acid had a liver lipid content of 12.9% to 31.9%, as compared with 3.8% to 19.4% of fat in the group on Diet 1, supplemented with the orange juice. There is no difference in longevity between these two groups. Therefore, a slight favorable effect on the liver lipids is noted in this experiment by using orange juice as the antiscorbutic factor. However, the two groups of animals on Diet 2 do not show this favorable effect of orange juice. Thus the group supplemented with orange juice have a liver lipid content of 12.5% to 34% and the group supplemented with pure ascorbic acid gives figures of 7.5% to 34%. However, the interesting thing in the group on the enriched Diet 2 supplemented with orange juice is their longevity. Only 1 animal

died after 63 days, 2 died after 200 days and 1 was sacrificed after 11 months. Apparently, the diet enriched with yeast and dextrose and supplemented with orange juice tends to keep the animals in an improved state of health and thus overcomes the deleterious effect of the fatty liver for a longer period of time. There seems to be a rough proportion between the survival time and the amount of fat in the liver. That is, the longer the animal survives on this diet the more fat will be deposited in the liver. There is one conspicuous exception to this apparent relationship. Animal 2 EM 6 (Table 2) was sacrificed after 300 days and the liver lipids were only 12.5%. However, this animal did not die spontaneously and this may have something to do with the relatively low fat content.

Effect of Lipocaic* and Choline on Liver Fat (Table 3). Because of the known lipotropic effect of choline[1-3,5,11] and the lipotropic effect obtained by Dragstedt[6,7,15] and his co-workers with a pancreatic extract (lipocaic), we used these substances in a group of experiments. We repeated the experiment of Table 1. That is, we permitted the animals to die of scurvy on Diet 1 but administered daily to each animal of a group 20 mg. of choline; and to each animal of another group, 475 mg. of lipocaic. These substances were dissolved in water and administered by mouth with a syringe.

TABLE 3.—INFLUENCE OF LIPOCAIC AND CHOLINE ON LIVER FAT.

Serial No. of animal.	No. of days on Diet 1.	No. of days Vitamin C-free.	% liver of body weight.	Mg. lipids per 1 gm. liver tissue.
	Controls.			
IM 1	47	25	10.5	238.8
IM 2	50	28	9.3	260.9
IM 4	49	27	8.0	109.3
IM 5	50	28	7.7	117.9
IM 6	52	30	6.9	122.1
	Lipocaic.			
1 LM 1	54	21	5.05	106.8
1 LM 2	55	22	6.4	108.1
1 LM 3	61	28	6.7	223.0
1 LF 4	48	15	8.3	128.3
1 LM 5	51	18	5.7	91.8
	Choline.			
1 CM 1	70	20	7.6	107.6
1 CM 2	66	16	7.1	127.8
1 CM 3	72	22	7.1	196.0
1 CF 4	39	39	...	42.8
1 CF 5	70	20	6.1	67.4

The influence of lipocaic on the deposition of fat in the liver of our animals was practically negative. The animals receiving lipocaic had total liver lipids varying from 9.1% to 22.3%, while the controls varied from 10.9% to 26%. This slight decrease can certainly

* The lipocaic used in these experiments was obtained through the courtesy of Eli Lilly & Co., for which we wish to express our gratitude.

be of no significance. With the choline supplement the results were somewhat lower; that is, from 6.7% to 19.6%, if we leave out 1 animal with a liver lipid of only 4.2% which died only 39 days after the experiment was begun. The other 4 animals were on the experiment longer than the controls or those on lipocaic and would be expected to have more fatty livers. So it appears that the choline may have a slight but certainly not spectacular effect on reducing the liver lipids in these animals.

Effects of This Diet on Other Species of Animals. Diet 1 has also been used by us on rabbits and rats. The rabbits like the guinea pigs acquired pathologic changes in the liver after being on the diet for some time. While increased fat in the liver was one of the findings, the tendency toward increasing fibrosis was more striking in this species. It will be noted (Table 4) that RM 2 was sacrificed after 148 days on this diet and had 24% of fat in the liver. RM 4 and RM 5 survived longer but had less fat in the liver, namely 5.3% and 9.8% respectively. It is likely that the fibrous tissue begins to replace the lipids as the pathologic process progresses. All the rabbits except the 2 that survived only 21 and 24 days had significant increase of fibrous tissue; 1 of these (RM 5) had a nodular liver which will be described below.

TABLE 4.—INFLUENCE OF DIET ON THE DEPOSITION OF FAT IN THE LIVERS OF RABBITS.

Serial No. of animal.	Diet.		% of liver of body weight.	Mg. lipids per 1 gm. liver tissue.
	Type.	No. of days.		
RN 1	Normal	...	..	11.7
RM 2	1*	24	4.0	13.9
RF 1	1	148	4.6	240.6
RM 3	1	21	3.04	22.3
RM 4	1	160	4.38	53.1
RM 5	1	281	4.05	97.9

* The diet in the rabbits was not supplemented by ascorbic acid. This species synthesizes vitamin C.

Albino rats do not appear to get fatty livers or develop fibrous tissue in the liver on this diet. None of the rats that died on this diet showed any significant liver changes, although some of these survived over 5 months.

Pathologic Picture. Grossly, the fatty livers in the guinea pigs were increased in size, extending down to the mid-abdomen, and were soft in consistency. The percentage of the liver to the total body weight in the normal and fasting animals was 4% to 5%; in animals with fatty livers, it was as high as 11.3%. The organ was yellow throughout with brownish punctate areas of the vascular channels. In the livers with less fat, the yellow areas alternated with pale reddish-brown areas more closely approximating normal liver tissue. It is interesting to note that in some of these animals, in spite of a loss of 30% to 40% of their body weight and the dis-

appearance of the normal fat depots, the liver contained an excessive amount of fat. For example, 1 animal on Diet 1, dying from scurvy, lost 41% of its body weight and yet the liver had nearly 24% of fat. This is of further importance since, as has been pointed out by Wells,[21] the production of fatty changes in the liver and other organs by poisons is interfered with by emaciation of the animal.

TABLE 5.—DIET 1.

	Parts by weight in gm.
Rolled oats, Wheat bran ½ and ½ by volume	59
Powdered milk, dried	30
Butter fat, melted	8
Cod-liver oil	2
NaCl	1

DIET 2.

Rolled oats, Wheat bran ½ and ½ by volume	48
Powdered milk, dried	30
Butter fat, melted	8
Cod-liver oil	2
Dextrose	10
Desiccated Brewer's yeast	1
NaCl	1

Microscopically, the parenchymatous cells of entire lobules were seen to be filled with fat globules (Figs. 1 and 2). With the Sudan 3 stain, the tissue was almost a solid orange color. In the severe cases the cytoplasm of nearly all the cells consisted of one or several globules of fat with the nucleus pushed over to one side, dark staining and pyknotic. In other cells the fat globules were more finely divided but clearly visible under higher magnification. The fatty replacement was usually more severe at the periphery of the lobule. In many of the animals surviving for a long period, a creeping in of fibrous tissue into the lobule was noted (Fig. 1). The histology of the liver in the various groups of animals varied only quantitatively, depending upon the amount of fat present. In 1 guinea pig (EM 2, Table 2) the liver was large (11.3% of the body weight), firm, and finely nodular. The abdominal wall was edematous and 25 cc. of ascitic fluid was present in the peritoneal cavity. Microscopically, in addition to liver cells filled with fat, there was a conspicuous increase in fibrous tissue as demonstrated by the Mallory stain (Fig. 3). The fibrosis was especially evident around the portal radicals. Here and there, there were islets of regenerating hepatic cells. It would seem justifiable to conclude that this guinea pig had developed a cirrhosis.

The most frequent other pathologic finding and one that was probably the most frequent immediate cause of death in the animals not dying from scurvy was patchy pneumonia, sometimes lobar in distribution. Ulcerative lesions of the stomach were also noted;

these were usually multiple, and most commonly located on the greater curvature.

In the rabbits in addition to the fatty changes in the liver, there was an increase in the interlobular connective tissue. In 1 rabbit (RM 5) the liver was grossly nodular and hard (Fig. 4). The liver was cut with difficulty and emitted a grating sound. Microscopically, the organ shows pseudolobulation, the normal liver architecture having been obliterated. The pseudolobules are bounded by thick bands of connective tissue. The connective tissue also proliferated between individual liver cords. The cytoplasm of the liver cells appears highly granular and the nuclei pyknotic (Fig. 5). This animal was sacrificed after 9 months. It seems likely that had this animal been allowed to continue living, the process would have progressed to ascites and other evidence of hepatic cirrhosis. In the rabbits, the percentage of the liver to body weight was not as markedly increased as in the guinea pigs.

Discussion. The development of liver changes in an animal receiving an "adequate" diet leads one to wonder whether our conception of such a diet is not an erroneous one. The diets we used contain an abundance of carbohydrates in the oats and wheat bran and the pure dextrose in Diet 2. A sufficient amount of complete protein is available in the casein of the powdered milk and in the oats. Although the fat is about 20% of the diet, it is only one-half as much as in the diet of Best and others,[1,2,11] who produced fatty livers in the rats by dietary means. Also the protein of their diets was about 5%, while the protein in our diets was nearly 25%. As was mentioned before, the rats on our diet did not develop fatty livers. An abundance of vitamins A and D is assured by the butter fat and cod-liver oil. The B complex is found in the cereal, and in Diet 2 is supplemented with yeast. Vitamin E is present in appreciable amounts in the wheat and oats and to a lesser extent in the butter fat. Hence the addition of ascorbic acid makes this an "adequate" diet from our present conceptions. However, since no toxins were introduced to damage the liver, we can only conclude that the diet was the sole responsible factor for this pathologic change. The possibility suggests itself that some little understood or unknown factor is absent from this artificial diet and may be present in the "normal" diet of the animal which contains leafy

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LEGENDS FOR FIGS. 1, 2 AND 3.

FIG. 1.—Liver lobule showing large globules of fat in the parenchymal cells. The fat globules increase in size toward the periphery of the lobule. Arrows point to fibrous tissue invasion. Guinea pig IM1 (24% fat). (H. and E., ×100.)

FIG. 2.—Fatty liver (H. P., mag. ×450) stained with Sudan III, which appears gray here.

FIG. 3.—Cirrhosis o the liver in guinea pig EM1. Note the large amount of fibrous tissue (arrows), fat, and regenerating liver cells in lower right corner. (Mallory stain, ×200.)

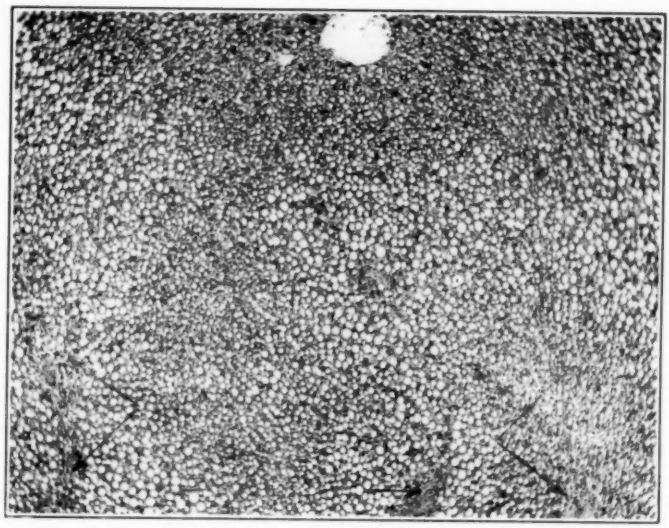

FIG. 1

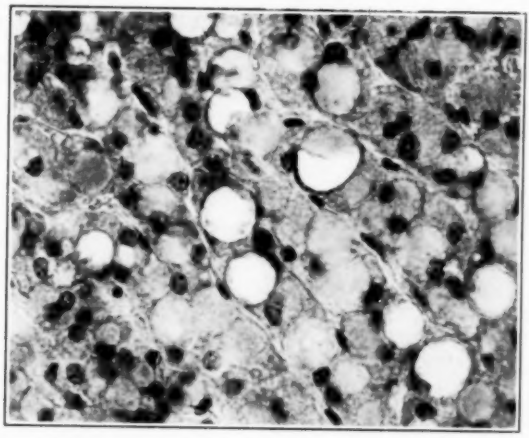

FIG. 2

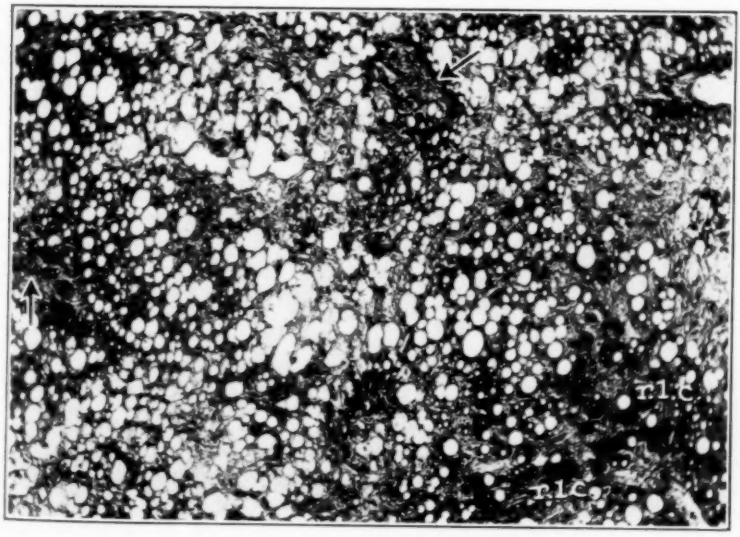

FIG. 3

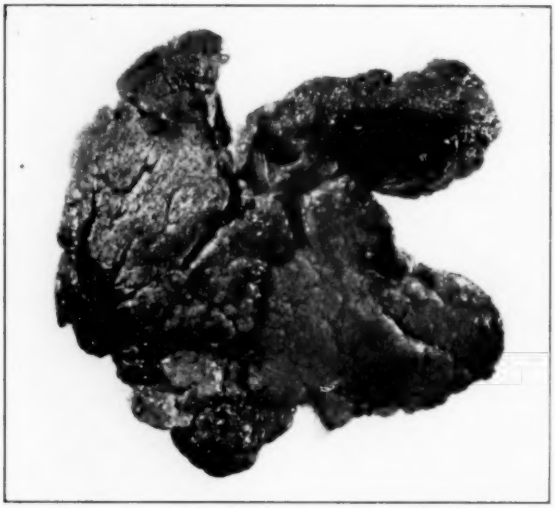

FIG. 4.—Cirrhotic liver of rabbit (RM5). Note the nodules, especially at lower edge, and the irregular surface.

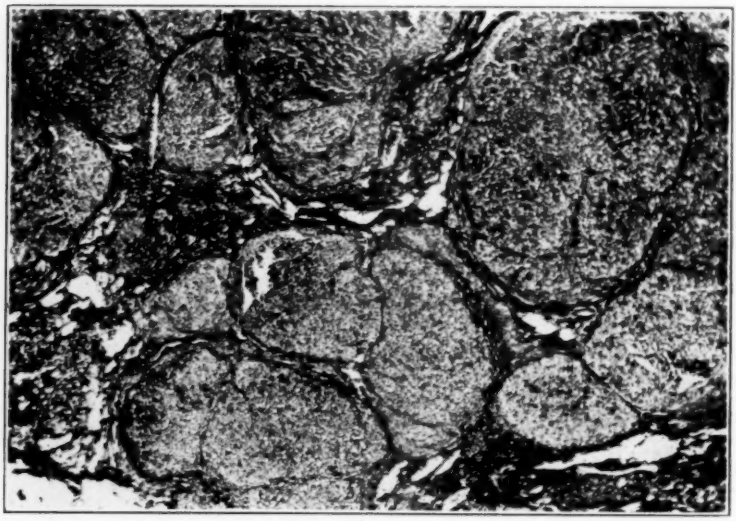

FIG. 5.—Cirrhotic liver of rabbit RM5. Note pseudolobulation, with fibrous tissue boundaries. Fibrous tissue replacing liver parenchyma (left lower corner). (×40.)

and/or green vegetables and carrots. It is certain, however, that this factor was not present in sufficient amounts in the orange juice given for its antiscorbutic effect. Neither is this unknown factor introduced in the 1% desiccated brewer's yeast supplement.

The typical liver cirrhosis produced in 1 guinea pig and 1 rabbit further suggests the relation of this diet to liver damage. It is known that cirrhosis of the liver is a chronic and slow-developing lesion and very frequently preceded by fatty degeneration.[19] We feel that our experiments may be throwing some light on the pathogenesis of portal cirrhosis in the human being. Patients that succumb to this lesion are not only consumers of large quantities of alcohol but are also neglectful of their diet. Patek[14] and others[19] have recently emphasized the therapeutic values of high vitamin feeding in clinical cases of "alcoholic" cirrhosis.

We are still in the dark as to the exact factor that is responsible for these changes but we are continuing the investigation. In addition to supplementing the diet with other foods that may contain the deficient factor, we are also decreasing the amount of fat in the basal diet. These animals may possibly be intolerant even to this moderate amount of fat. Gyorgy and Goldblatt[9] reported hepatic damage in rats on a diet that is deficient in one of the obscure fractions of the B complex, since the known factors did not prevent this damage. However, they admit that this lesion was not always predictable, and the pathologic changes were variable, only occasionally was fatty metamorphosis conspicuous. Their diet did not contain any cereal foods, such as is present in our diets. These foods (oats, wheat bran) are supposed to contain the complete B complex.

The effectiveness of choline as a lipotropic agent first became known because of its effect on the liver fat of depancreatized dogs.[3] Later, it was also shown that this substance is effective in preventing and curing the fatty livers produced by low protein and high fat diets in the rat.[1,2,11] Our animals satisfied neither of these conditions; they were not depancreatized nor was the diet poor in proteins. According to Best[2] 1 gm. of casein contains about 5 mg. of choline. With 30% skimmed milk powder in our diet, the amount of choline would appear to be sufficient. We administered an additional 20 mg. of pure choline to our animals daily, which in itself should be sufficient, since 5.6 mg. was found to be an adequate amount for 150 gm. rats on the low protein diet.[2] While the animals on choline showed some slight drop in liver fat as compared with the controls, the difference is not sufficient to make it likely that choline is the essential factor in this phenomenon.

Dragstedt and his co-workers[6,7,15] claim that their pancreatic extract contains a hormone, elaborated by the pancreas, which has a controlling effect on lipid metabolism and especially on the deposition of fat in the liver. Best and Ridehout[2] have shown

that the lipotropic effect of lipocaic on rats maintained on low protein diet can be explained on the basis of its choline content. Aylward and Holt[1] came to the same conclusion in rat experiments. Montgomery, Enteman and Chaikoff[13] and Ralli and coworkers[16] were able to produce fatty livers in dogs by ligating the external pancreatic ducts, thereby throwing doubt on the theory that an internal secretion is responsible for the deposition of fat in the depancreatized dog's liver. Without intending to enter into the controversy of the hormonal nature of lipocaic, we wanted to determine the influence of this pancreatic extract on our experimental animals. The administration of 475 mg. daily to a 500 gm. guinea pig was thought to be sufficient in view of Dragstedt's[7] earlier statement that 1.5 gm. of the extract was enough to prevent fatty liver in dogs probably weighing 20 times as much. The negative effect of the extract on our animals proves to us that this extract is not effective in preventing the fatty livers in our experimental animals.

Summary and Conclusions. 1. Fatty degeneration of the liver has been produced in the guinea pig and rabbit by apparently adequate diets, devoid of vitamin C.

2. Neither pure ascorbic acid nor orange juice has any prophylactic effect on this pathologic change.

3. An addition of 1% desiccated yeast and 10% dextrose was without effect.

4. Twenty milligrams of choline administered daily has slight effect in preventing deposition of fat in liver, while 475 mg. lipocaic was ineffectual.

5. Cirrhosis of the liver was produced in 1 rabbit and 1 guinea pig.

6. Some dietary factor is responsible for the development of the fatty degeneration and the cirrhosis. By implication, cirrhosis in man also may be due to a dietary deficiency.

7. Investigation is being continued to clear up some of the questions raised.

Addendum. After the completion of the above investigation, a recent publication by Rich and Hamilton[17] came to our attention. These workers report the production of fibrotic livers in rabbits on diets deficient in the B complex. On December 7, 1939 we put 4 guinea pigs on a diet which, in addition to the other ingredients, contained 10% desiccated brewer's yeast. One of these animals died April 20 and its liver contained 39% fat. The other animals are still (June 10, 1940) in good health and are taking the diet well.

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ENDEMIC RIBOFLAVIN DEFICIENCY IN INFANTS AND CHILDREN.*

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Little could Blyth have realized in 1879,[1] when he described the yellow-green fluorescent pigment of whey, that brilliant research by a number of investigators in the years to come would show that it is an accessory food substance essential to the health and well-being of the higher forms of life. With the artificial synthesis of riboflavin in 1937, a milestone in the chemical research was passed, and this achievement opened a new vista for clinical investigation. Soon after it was synthesized it became available in sufficient quantities for clinical investigation, and during the past 18 months several reports on the effect of a deficiency of riboflavin in human beings have appeared in the medical literature.[2,3,6a,b,10,12] Although these reports are concerned with the disease in adults, it occurs in any age group, and from our studies we are convinced that among malnourished children diagnostic lesions of the disease are more common in the southern part of the United States than those of any other deficiency syndrome.

During the past 5 years we have been studying the natural course of development of deficiency diseases in an area in which they are endemic. In so doing, we have made clinical, laboratory and dietary studies of the entire family rather than of the individual patient,

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for within the family each member in general is subjected to the same dietary deficiencies. The information presented here will be restricted to that obtained from the study of infants and children who had diagnostic evidence of riboflavin deficiency.

During a period of 2 years, 472 children of parents with deficiency diseases were examined repeatedly, with particular attention directed toward their physical and mental development and toward the presence or absence of lesions characteristic of riboflavin deficiency. Without using special instruments or tests, we made a clinical diagnosis in each instance if one or more of the lesions characteristic of this deficiency were present. These lesions which in children appear similar to those seen in adults, include "cheilosis," the reddened macerated areas at the angles of the mouth and the linear lesions first described as responding to riboflavin by Sebrell and Butler,[6a] and the ocular symptoms characterized by bulbar conjunctivitis, lacrimation, burning of the eyes and failing vision, first found to respond to riboflavin by Spies, Vilter and Ashe.[10]

In children ranging in age from 5 months to 14 years we observed cheilosis in 113 cases, linear lesions in 93, and ocular manifestations in 167. These children were usually underweight, under-developed for their age. Many of them were apathetic and indifferent and had made poor progress in school. Frequently they complained of their mouths being sore and of their eyes burning and itching. The order of appearance of these symptoms was extremely variable and all did not occur in every case. Some children with advanced lesions of the eyes had no lesions of the corners of the mouth; others had severe mouth lesions whereas the eye lesions were slight. All these symptoms waxed and waned with the seasons and with changes in the quality of the dietary but they appeared most frequently during the spring and summer. Increased exercise and infections seemed to precipitate the appearance of lesions in the borderline cases. The response of children with riboflavin deficiency to synthetic riboflavin or to substances rich in it was gratifying. The cheilosis healed rapidly, the ocular symptoms disappeared, and the general health of the children improved. Unless therapy was continued or the diet improved, the disease tended to recur. The order of reappearance of the symptoms in any given patient invariably went through the same sequence with each recurrence, yet they varied greatly from patient to patient.

Laboratory studies showed that riboflavin is a normal excretory product when the diet is adequate, but when a severe deficiency exists the amount excreted is greatly diminished.[9] When the dietary intake is very low the excretion may for a time exceed the intake and, conversely, on a high intake the excretion may lag behind. In the absence of therapy, all the patients with advanced diagnostic lesions excreted less than normal persons of the same age, sex and size. Smears and cultures taken from the fissures at the

FIG. 1.—Note cheilosis at either angle of the mouth and the rather deep linear fissures of the lower lip.

FIG. 2.—Note the violet hue of the eyes, which is most discernible in the right eye, and particularly the injection at the corners.

angles of the mouth showed either pure or nearly pure cultures of hemolytic *Staph. aureus* in 80% of the cases; *Strep. hemolyticus* was the predominant organism in the remaining 20% of the cases.[5] Hemolytic strains of *Staph. aureus* were isolated in 14 of 30 cases of conjunctivitis. *Corynebacterium xerosis* was found in a high percentage of the cases and was obtained in pure culture from the spots of Bitot in all of the 5 cases having these spots.[4]

The dietary studies showed that almost without exception the mothers of these children had subsisted on grossly inadequate diets during pregnancy and lactation. In some cases the mother's milk supply had been so meager that the infant was weaned soon after birth and given food which was inadequate for its nutritional needs, while in others the child nursed until it was 2 or 3 years of age. In every instance, they began eating food from the family food supply at the age of 2 or 3 months and were allowed to choose whatever foods they desired. The foods usually selected, because they are the ones most commonly used by the family, were biscuit, cornbread, gravy and syrup. Such foods habits had become firmly established at an early age and we found them difficult to change. Realizing that riboflavin is widely distributed in natural foodstuffs, at first thought we were surprised to find a deficiency of this substance so common. However, repeated dietary studies showed that the majority of infants and children in our study received only 35% of their estimated requirement.[8]

The following representative case history describes clinical riboflavin deficiency in a 14-year-old boy, and his response to treatment with brewers' yeast while he continued to eat his usual inadequate diet.

Case 1.—C. A., the oldest of 8 children in a family in which the mother and father and each of the other children had lesions characteristic of riboflavin deficiency, was first seen June 8, 1940. He complained of soreness of the mouth, itching and burning of the eyes, and general weakness. This boy, like all other members of the family, subsisted on a diet consisting of bread, grits, dried beans, salt pork and syrup. The family occasionally had fruit, but never ate green vegetables. At times when milk and eggs were available, the children drank 1 or 2 glasses of milk and ate 1 or 2 eggs daily, but these foods were unavailable for months at a time.

Physical examination showed characteristic lesions of riboflavin deficiency, as evidenced by a large macerated area, 0.5 cm. across, at each corner of the mouth, at the outer edge of which a yellow crust had formed. A few superficial linear lesions were present on the lower lip (Fig. 1). The conjunctival vessels were greatly dilated and reddened, and the boy rubbed his eyes frequently. He had blepharospasm, and the injection of each eye was more pronounced in the lower half than in the upper half (Fig. 2). The inner surfaces of the lids were fiery red. No therapy was given the first week and it was observed that the lesions became worse. Riboflavin determinations on the blood, made by Miss Sue R. Stanbery, showed that his blood contained 0.32 gamma per cc. in contrast to the normal of 0.4 gamma per cc., as determined by the lacto-bacillus caseii technique of Snell, Strong and Peterson.[7]

The patient was given 10 brewers' yeast tablets (Mead Johnson and Co.) t.i.d. (equivalent to 1 ounce of dried brewers' yeast). Within 5 days there was striking healing of the lesions around the mouth and in the eyes, despite the fact that throughout the study there had been no change in his dietary. The brewers' yeast supplement was discontinued and the dietary intake remained constant, and within 2 weeks there was a beginning recurrence of the lesions. The yeast tablets were again given in similar dosage, and the symptoms disappeared within 48 hours.

The following case shows clearly the development of riboflavin deficiency in a nursing infant and the response of both the mother and the infant following the administration of synthetic riboflavin to the mother without any change in the general dietary. It is of interest that the child also had a severe diarrhea of the type described by Spies, Walker and Woods.[11] The prompt relief of the child's diarrhea by giving the mother nicotinic acid indicates that the mother and certainly the child had nicotinic acid deficiency as well as riboflavin deficiency, though there were no lesions diagnostic of pellagra.

Case 2.—Mrs. M. E., a 30-year-old white woman, came to the Nutrition Clinic of the Hillman Hospital July 2, 1940, complaining of weakness, headaches, nervousness and a sore mouth which had been present since the first of May. She brought her 23-month-old child, the youngest of 4 living children. The following history was given by the mother:

The child's maternal great-grandmother and 3 aunts had died of pellagra. For years the family dietary had consisted of large amounts of cornbread and biscuit and moderate amounts of dried vegetables, sugar, desserts and fat meat. During the summer they ate green vegetables 4 or 5 times a week. They drank buttermilk when they could get it, which was infrequently, and had not had any since the first of April. Each member of the family except the baby had an average of 2 eggs a week. They rarely had lean meat and never used butter. The mother complained of having been weak, nervous and irritable for several years, particularly in the spring and summer. For the last 14 years she had been pregnant or lactating or both, and she usually nursed her children until they were 24 months of age. Her first attack of clinical pellagra occurred in 1937 when she had been nursing her fifth child for approximately a year. In 1938 she had pellagrous dermatitis over her hands, forearms and arms.

Physical examination revealed a poorly developed, poorly nourished woman weighing 96 pounds. Her conjunctivæ were injected, as were the canals and bony landmarks of her ears. There was a whitish macerated area characteristic of riboflavin deficiency at each angle of her mouth. She was observed weekly over a period of 5 weeks, during which time the oral and ocular lesions became much worse. At the end of this time she was given orally 10 mg. of synthetic riboflavin (Mead Johnson and Co.) daily, and her diet remained unchanged. Within 2 weeks after therapy was initiated, the angles of her mouth had healed, the ocular lesions had improved, and she felt strong enough to do her own housework.

R. E., the 20-month-old daughter, had been on breast milk since birth, supplemented with biscuit, cereal, candy and sugar which she began eating at the age of 4 or 5 months. On a few occasions she was given orange juice. All spring she had been irritable and cross, and 2 months before she was seen in the Nutrition Clinic of the Hillman Hospital she began having intermittent diarrhea. (The diarrhea became much more severe during the next month.) When she was seen in the clinic, she had

cracks and fissures at the angles of her mouth, characteristic of riboflavin deficiency. Although the child was not treated, her lesions healed completely within 1 week after the mother's treatment was begun, a week earlier than those of the mother. The diarrhea continued but was relieved 1 week later following the administration of nicotinic acid to the mother.

Summary and Conclusions. 1. Repeated clinical, laboratory and dietary studies on 241 infants and children having characteristic riboflavin deficiency have convinced us that it is the most common clinical deficiency disease among infants and children in an area in Alabama in which deficiency diseases are endemic.

2. The mothers of these children usually subsisted on inadequate diets during pregnancy and lactation, and specific treatment of the mother with riboflavin or substances rich in riboflavin was curative for the lesions in the nursing infant.

3. Our studies indicate that riboflavin deficiency is a non-contagious, non-hereditary disease which occurs in either sex of any race. It develops over months and years, and the appearance of diagnostic lesions is preceded by a period of ill-health which should properly be termed the deficiency development time.

4. The response to specific therapy is gratifying in that every case was relieved by the judicious use of one of the specific therapeutic agents. Following therapy there is an increase in vigor and in sense of well-being and, in many instances, a striking increase in growth. The ocular manifestations disappear and the lesions around the mouth heal. As such lesions heal it becomes impossible to demonstrate the presence of *Staph. aureus hemolyticus* and *Strep. hemolyticus* which were prevalent before therapy.

5. The morbidity rate is greatly decreased when the physician makes the diagnosis early and initiates therapy. We find that the average case responds satisfactorily to the oral administration of 1 mg. of riboflavin t.i.d. or 1 ounce of brewers' yeast or liver extract daily. These substances have been given a sufficient period of time to warrant no hesitancy in recommending them as safe and effective therapeutic agents for the treatment of mother, infant and child. Despite the fact that the lesions of riboflavin deficiency were relieved while the general diet remained the same, we recommend the addition of liver, lean meat, and milk whenever possible.

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BOOK REVIEWS AND NOTICES

HEART FAILURE. By ARTHUR M. FISHBERG, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 829; 25 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $8.50.

THE many merits that marked the first edition and made it an excellent and valuable book have been maintained in this enlarged edition. The book is practical, in a sense that will appeal to the practicing physician. The full and critical presentation of much physiologic and experimental data, upon which our modern conceptions of the nature of heart failure are based, also makes it a book of reference for the more specialized student of the circulation. T. M.

PNEUMONIA. With Special Reference to Pneumococcus Lobar Pneumonia. By RODERICK HEFFRON, M.D., Medical Associate, The Commonwealth Fund; Formerly Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 1086; 18 figures, 181 tables and several maps. New York: The Commonwealth Fund, 1939. Price, $4.50.

THIS imposing volume presents a comprehensive discussion of pneumonia, especially of pneumococcus lobar pneumonia, and the treatment of that condition. It is in part the outcome of the work of the Massachusetts Pneumonia Study. In the preparation of the book a very extensive literature was consulted and abstracted: there are cited nearly 1500 references. One finds here a thorough review of investigations dealing with the etiologic agent, its method of transmission, therapeutic measures, and the factors influencing recovery. This phase of the work will be gratefully received by the many workers in this active and vital subject. Yet so rapid is current progress in this field, that a supplement is already in order, for there are only 26 references to articles appearing in 1938, and none since that time. Nevertheless, the completeness of the material in all other respects and its well-balanced presentation stamp this as the outstanding and authoritative work on pneumonia. R. K.

THE HEAD AND NECK IN ROENTGEN DIAGNOSIS. By HENRY K. PANCOAST, M.D., Late Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania, EUGENE P. PENDERGRASS, M.D., Professor of Radiology, and Director of the Department of Radiology, University of Pennsylvania, and J. PARSONS SCHAEFFER, M.D., PH.D., Professor of Anatomy and Director of the Daniel Baugh Institute of Anatomy, Jefferson Medical College. Pp. 976; 1251 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $12.50.

THIS publication is a volume of 976 pages which covers the Roentgen diagnosis of diseases affecting the head and neck very thoroughly. Included are 1200 illustrations of which more than 700 are negative prints of roentgenograms and photographs of patients and of basic technical procedures. Over 300 are illustrations which depict very clearly the anatomy of the head and neck and which show new aspects of these anatomic structures.

In the first chapter, the anatomy of the skull is described. The following chapters are devoted to fractures and dislocations; diseases of bone affecting the skull; tumors of the scalp, skull and cervical spine; the teeth and jaws; the nose and lacrimal passages; the paranasal sinuses; the temporal bone and affections of the mastoid and petrosa; intraorbital foreign bodies; intracranial tumors and cerebral pneumography. The last two chapters cover conditions affecting the cervical spine and neck.

The collaboration of the roentgenologist and the anatomist makes the volume especially valuable as there is no necessity for consultation of textbooks of anatomy, and in many cases the rationale of roentgen interpretation and procedure is made much clearer than would be otherwise possible. The anatomic illustrations are well chosen with this end in view. The authors in their preface state that, possibly, errors in judgment in selection of material may be noted. No such criticism, however, seems to be justifiable. For instance, the exclusion of variations in the skull occurring in the rare type of chondrodystrophy, known as gargoylism, cannot be regarded as of serious consequence. In fact, the omission of rarely occurring pathologic processes is of very infrequent occurrence, and as a comprehensive reference and textbook it cannot be recommended too highly. The effort of the authors to include only relevant facts and descriptions is reflected throughout the book. The bibliography at the end of each chapter is sufficient to afford the student ample opportunity to consult original source material. Of especial worth are the chapters on intracranial tumors, cerebral pneumography and the paranasal sinuses. The book is well printed and the illustrations are uniformly excellent and clear. The text shows careful editing with freedom from typographical errors.

After the illness and death of Dr. Pancoast, the burden of collection and composition of the roentgenologic portions of the book devolved upon Dr. Pendergrass. His long, painstaking labor is well rewarded by this publication of the finished product. The volume should be included in the library of every roentgenologist and it is most valuable, too, as a source of information on roentgen interpretation for the neurosurgeon, the otolaryngologist and other specialists. R. B.

AN INTRODUCTION TO BIOCHEMISTRY. By WILLIAM ROBERT FEARON, M.A., Sc.D., M.B., F.I.C., Fellow of Trinity College, Dublin; Member of the Royal Irish Academy. Pp. 475. Second Edition. St. Louis: The C. V. Mosby Company, 1940. Price, $3.75.

THE American Edition of this book will be found valuable for students and teachers of biochemistry and as a reference book for practitioners of medicine. Although laboratory tests are included, nevertheless, the book is not intended primarily as a laboratory manual. The approach is different from the usual textbooks of biochemistry—the opening chapters being devoted to a description of the properties, occurrence and significance of the components of biologic materials. Included in this edition are special chapters on Steroids, Pigments (Pyrrole Derivatives, Carotinoids and Flavins) and Tissue Respiration. F. S.

THE RELATIVITY OF REALITY. By RENÉ LAFORGUE, M.D. Translated by ANNE JOUARD. Pp. 92. New York: Nervous and Mental Disease Monographs, 1940. Price, $2.50.

THIS book deals with the following clinical psychoanalytic subjects: Concerning Anxiety, Conflicts in the Affective Development of Man, Relativity of Reality and Genesis of the Need of Causality, Reflections Concerning the Intellect, and Reflections on the Notions of Free Will, Liberty and Death. Anxiety is definitely in the foreground in phobias and hypo-

chondriasis, whereas it is in the background of obsessions, hysteria, paranoia, schizophrenia and frustration neuroses. Anxiety is an emotional state from which the individual attempts to escape. It may be normal and due to real danger, or neurotic, arising from the individual's peculiar psychic conflicts. Repression of the pathologic type is termed *scotomatization*. While Freud did not create psychoanalysis, he glorified it and his teachings for the most part are followed here. An exception is his statement that relation is an "illusion." The author says: ". . . . religious beliefs appear from the psychoanalytic view point, as a necessary aspect of affective development, an aspect corresponding to reality which no scientific argument can devaluate." Speaking of Einstein's relativity of time and space, the writer says: "We have ourselves added to this notion that of the relativity of reason, of truth or logic, of science . . . . those concepts found to be of value to man, in ways economic as well as political and social."

This is an interesting contribution to psychoanalytic literature.

N. Y.

THE PATIENT IS THE UNIT OF PRACTICE. By DUANE WILLARD PROPST, A.B., B.S., M.D., Assistant Professor of Medicine, University of Illinois, College of Medicine. Pp. 219; 4 plates. Springfield, Ill.: Charles C Thomas, 1939. Price, $3.50.

THIS book is a curious though at times interesting mélange of observations and reflections on the nature of disease, the defenses of the body, the elementary principles of psychobiology, an attempt to systematize physical diagnosis, a detailed account of history taking, and finally the author's diagnosis and treatment of many cases—mainly cases which presented organic symptoms but were best treated by psychiatric methods.

One wonders whether the author has attempted to arrange systematically a series of clinical lectures on a variety of topics, but for the sake of extended exposition in book form has added to the originals those features of his reading which have impressed him most. One notes that his hobbies include the constitutional background of susceptibility to disease and particularly the psychosomatic approach to diagnosis and treatment.

The book is entertaining but at times confusing. It may stimulate the student to look behind the presenting organic symptoms but not to investigate fundamental problems.

E. T. JR.

PRACTICAL CLINICAL PSYCHIATRY. By EDWARD A. STRECKER, A.M., SC.D., M.D., Professor of Psychiatry and Chairman of the Department of Psychiatry, School of Medicine, University of Pennsylvania, etc., and FRANKLIN G. EBAUGH, A.B., M.D., Professor of Psychiatry, University of Colorado Medical School, etc. Section on Psychopathological Problems of Childhood. By LEO KANNER, M.D., Associate Professor of Psychiatry, Johns Hopkins University School of Medicine. Pp. 728; 55 figures. Fifth edition. Philadelphia: The Blakiston Company, 1940. Price, $5.00.

THESE recognized authorities give considerable more attention to the psychobiologic hypothesis of Adolph Meyer in this edition, than in the preceding one. A well written chapter on the Psychopathological Problems of Childhood is included, and much additional matter on therapy and psychopathology is added. Whenever practicable, the case method is employed. On page 277, within four lines, marijuana is twice misspelled—mariahuana and marihuana; common usage may justify the spelling of the latter, but not the repeated use of the former. There now being many extra-mural psychiatrists, the Reviewer suggests the inclusion of some formal consideration of criminology, in the so-called complete text-books on psychiatry. This is a thoroughly revised edition of a deservedly popular text-book.

N. Y.

THE DIAGNOSIS AND TREATMENT OF PULMONARY TUBERCULOSIS. By JOHN B. HAWES, 2D, M.D., late President of the Boston Tuberculosis Association; Director of the National Tuberculosis Association, etc., and MOSES J. STONE, M.D., Assistant Professor of Medicine, Boston University, School of Medicine; Physician to the Chest Clinic of the Massachusetts Memorial Hospital, Boston, Mass. Pp. 260; 75 illustrations. Second edition, revised by DR. MOSES J. STONE, with a Foreword by the late RICHARD C. CABOT, M.D. Philadelphia: Lea & Febiger, 1940. Price, $2.75.

THIS handbook has been written apparently for medical students and general practitioners who desire more information about the diagnosis and treatment of pulmonary tuberculosis than is available to them in single volume textbooks of medicine. The chapters devoted to the clinical aspects of tuberculosis offer less information than one might expect of even a small book written on this subject. Those concerned with treatment, particularly compression therapy, are sufficiently complete to serve as a useful source of reference. S. L.

A TEXTBOOK OF PHYSIOLOGY. By WILLIAM H. HOWELL, PH.D., M.D., Sc.D., LL.D., Emeritus Professor of Physiology in The Johns Hopkins University, Baltimore. Pp. 1117; 330 illustrations. Fourteenth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1940. Price, $7.50.

IN this latest edition of his well known text on mammalian physiology, Professor Howell has maintained the high standard of excellent organization and simplicity characteristic of his earlier editions. By condensation of certain sections he has been able to bring new material into the text without significantly altering the total reading matter. The revisions and additions in the main are as follows: The chapter on the chemistry of muscular contraction has been revised, and that on electrical phenomena has been enlarged to include a brief discussion of Spike and After-Potentials. The chapter on the cerebrum has been somewhat rewritten, and that on the autonomic nervous system to include a more detailed discussion of the chemical transmission theory. The section on the ear includes a discussion paragraph on the cochlear response and the action potentials of the auditory nerves, and the section on the theories of hearing has been rewritten. In this section the subject of blood coagulation has been revised and a short paragraph on "shock" has been added. The main revisions include the interweaving into the story of digestion the possible function of vitamin K, reclassification of the amino acids to bring the number of known acids to 27, and some revision of the chapters on the kidney and endocrine glands. The main revision of this section involves the chapter on vitamins, in addition the discussion on carbohydrate metabolism and diabetes has been rewritten. M. M.

ENDOCRINE THERAPY IN GENERAL PRACTICE. By E. L. SEVRINGHAUS, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin. Pp. 239; 49 illustrations. Chicago: The Year Book Publishers, Inc., 1940. Price, $2.75.

THE third edition of this monograph has been improved by revision. An excellent chapter on Endocrinopathies in Children and Adolescents has been added. It is the clearest and wisest presentation of endocrinology available for the student and practitioner. F. L.

NEW BOOKS.

Management of the Cardiac Patient. By WILLIAM G. LEAMAN, JR., M.D., F.A.C.P., Assistant Professor of Medicine in Charge of the Department of Cardiology, Woman's Medical College of Pennsylvania, Philadelphia; Cardiologist, Woman's College, Memorial, Northeastern Hospitals and Philadelphia Hospital for Contagious Diseases, etc. Pp. 705; 255 illustrations. Philadelphia: J. B. Lippincott Company, 1940. Price, $6.50.

Laboratory Text in Pharmacology. By ROBERT P. WALTON, Professor of Pharmacology, School of Medicine, University of Mississippi. Pp. 85. Philadelphia: J. B. Lippincott Company, 1940. Price, $1.50.

This collection of experimental exercises, each accompanied by a brief discussion, is intended to serve in a supplementary manner to the more complete laboratory manuals and standard texts. . . . . The exercises in many cases are of a demonstration character but they can be performed by student groups, particularly if the more involved demonstrations are given as special assignments well in advance of the scheduled periods. (From Preface.)

De Morbis Artificum Bernardini Ramazzini Diatriba. Diseases of Workers. The Latin text of 1713. Revised, with translation and notes by WILMER CAVE WRIGHT, Emeritus Professor of Greek in Bryn Mawr College. Pp. 549. Chicago: The University of Chicago Press, 1940. Price, $5.00.

The Author Publisher Printer Complex. By ROBERT S. GILL. Pp. 76. Baltimore: The Williams & Wilkins Company, 1940. Price, $1.00.

The Medical Clinics of North America, Vol. 24, No. 5 (Boston Number, September, 1940). Pp. 294; 22 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This Boston number is made up of two symposia—the one on cardiovascular diseases consisting of 6 articles; the longer one on "diagnostic hints," of 11 articles dealing with different systems of the body. The term has been very loosely interpreted by some of the authors.

Die Amputationen der Oberen Extremität. By HANS ISELIN-HAEGER, o. Professor für Unfallmedizin der Universität, Basel; FMH für Chirurgie, Orthopädie und Röntgenologie. Pp. 72; 66 illustrations. Basel: Benno Schwabe & Co., 1940. Price, Sw. Fr. 4.

The Chronicle of Crichton Royal (1833–1936). Being the Story of a Famous Mental Hospital During Its First Century, and Illustrating the Evolution of the Hospital Care and Treatment of Mental Invalids in Scotland. By CHARLES CROMHALL EASTERBROOK, M.A., M.D., F.R.C.P.E., Physician Superintendent, 1908–1937. With Foreword: Some Early Crichton Memories, by the late SIR JAMES CRICHTON-BROWNE, M.D., LL.D., F.R.S. Pp. 663; 103 illustrations and map. Dumfries, Scotland: Courier Press, 1940. Price, 25/-.

Edinburgh Post-Graduate Lectures in Medicine, Vol. 1, 1938–39. Pp. 513; illustrated. Edinburgh: Oliver and Boyd for the Honyman Gillespie Trust, 1940. Price, 10/6.

"A generous grant towards the promotion of post-graduate teaching received during the past two years from the Trustees of the late Mrs. Honyman Gillespie has been directly responsible for the appearance of this volume. . . . . Thirty-three lectures were delivered by authorities upon their respective subjects. Originally published in the *Edinburgh Medical Journal,* they have since been submitted to the lecturers for correction before republication in the present volume. . . . ." (From the Foreword.)

NEW EDITIONS.

Feeding the Family. By MARY SWARTZ ROSE, PH.D., Professor of Nutrition, Teachers College, Columbia University. Pp. 421; illustrated. Fourth Edition. New York: The Macmillan Company, 1940. Price, $3.75.

Food, Nutrition and Health. By E. V. MCCOLLUM, PH.D., Sc.D., and J. ERNESTINE BECKER, M.A., Professor, and Associate, of Biochemistry, School of Hygiene and Public Health, Johns Hopkins University, Baltimore. Pp. 127. Fifth Edition, entirely rewritten. Baltimore: By the Authors, 1940. Price, $1.50.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

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SHORT WAVE DIATHERMY.

TWELVE years have elapsed since Schereschewsky,[33] Schliephake,[34] and others first reported on biophysical and clinical observations with ultra-high frequency oscillations, also described as short waves. Since in therapeutics there are also employed longer and shorter waves of the ultraviolet, infra-red and Roentgen ray portions of the electromagnetic spectrum, one cannot correctly speak simply of short waves without further qualification. In their physical and physiological effects the "short" waves of 30 to 6 meters (10 to 50 million oscillations per second) are next of kin to the 300 meter waves of "conventional diathermy" (1 million oscillations per second), and consequently in the United States the terms short wave diathermy for the former and long wave diathermy for the latter has been generally accepted. Kowarschik[17b] and others abroad have recently acknowledged the logic of the American terminology. The distinction originally introduced between short and ultra short waves has been largely discontinued in recent years and replaced by a simple statement of the wave length employed.

Physical and Physiologic Effects. There still exists some controversy as to whether the primary physical effect of short wave diathermy is due to anything else than heat. A few observers have described "athermic" effects and some hold that these effects depend on the electro-specific innate qualities of the substances treated. Hasche[12] has recently shown that tissue cells consisting of cultures of embryonic chick fibroblasts and osteoblasts could be killed by short wave diathermy under experimental conditions in which destruction could not be attributed to heat. He holds that the destructive effect of short wave diathermy occurs through diffusion and osmosis without liberation of electrons in contrast to Roentgen and radium rays which act through electron bombardment. Dognon[8] likewise believes that certain phenomena

like stimulation or inhibition of cellular activity cannot be explained on the basis of the thermal factor only.

The great majority of observers, however, regard short wave diathermy as a specific form of heat therapy which differs from long wave diathermy chiefly in the mode and extent of passage through tissues. The most striking physical property of ultra high frequency oscillations is their ability to pass through electrically conductive as well as poor conductive tissues. The heating of non-conductive substances in short wave fields is based on the phenomenon of dielectric permeability, and the higher the dielectric constant of a given substance the higher will be the capacity or strength of the electric field. Patzold[29] states that because of both conductive and "capacitative" heating by short wave diathermy, parts of the body which are closed off with poor conductors (fat, bones, and so on) such as inner organs, the spinal cord and the brain, will share in absorbing the electrical energy and hence they can be warmed without overheating the good conductive tissues which lie around them. This occurs especially with the shorter wave lengths below 10 meters. However, the wave length *per se* is not a marked factor in tissue heating in the living subject, as shown by Coulter and Osborne,[4] because differences in machines, the energy delivered to the patient and the technique employed exert an equally important if not decisive rôle.

In the early stages of investigation much was written about the possibility of selective heating effects by short wave diathermy at certain depths and in certain organs. This was based on the original report of McLennan and Burton[22] that for a given wave length there is a maximum heating effect which has a definite relation to the specific conductivity and dielectric constant of tissues. However, it was correctly pointed out by Mortimer[26] that the blood flow and the rapid interchange of heat in the living body may render the differences in temperature negligible for all practical purposes. Schaefer[32] finds that the only instance of practical import in which distinct variation may exist between the various body tissues is that encountered in fatty tissue in which overheating may be avoided by using the shortest possible wave length.

Specific bactericidal action has been claimed in the early reports of Haase and Schliephake,[11] but subsequent investigations have failed to corroborate such effects. Ozzano and Re[28] found with several species of pathogenic bacteria that short wave irradiation sometimes stimulated and sometimes inhibited their development and concluded that short wave diathermy exerted no selective specific action on bacteria but acted abiotically by heating the bacteria's environment. Hasche, Leunig and Loch[13] reported similarly.

Schereschewsky's original communication reported on lethal action on transplantable sarcoma in mice and attributed this to a specific biologic effect. Subsequently, similar claims were made by Reiter.[31] H. and M. Langendorff[19] repeated Reiter's experiments on induced tumors and refuted the theory that certain wave lengths have a specific action on tumors; they also found that any effect on tumor tissues was solely due to a rise in temperature in them and concluded that better results might be expected in treatment of malignant tumors by combined short wave and Roentgen therapy. On the other hand, Baumeyer[2] showed that coincident short wave and Roentgen treatment could lead

to the enlargement of malignant tumors and that short wave therapy was therefore contraindicated for malignancies.

Summing up all evidence available at present, it would appear that tissue heating is the only proved biophysical effect of short wave applications. Hildebrandt[14] investigated pharmacologic effects with short waves, assuming that in addition to a thermal effect on the tissues, chemical changes are also produced. The histamine content of dogs' blood was examined after treating the thorax for one-half to one hour with 3.5 meter waves. Specimens of blood taken at various intervals showed an immediate increase of several hundred per cent in some, while in others the maximum was reached only after two hours. A gradual return to normal value ensued in all in the next few hours. Diathermic tests yielded virtually the same results. Hildebrandt attributes the influence of the histamine content of the blood to the pronounced thermal effect of the short wave current.

Clinical Applicability. The advantages of the new techniques with the airspaced and inductance coil technique have led to the general acceptance of short wave diathermy as a simple and safe method of penetrating tissue heating. Beginning with Schliephake's first communications long lists of pathologic conditions were published in which short wave diathermy had been employed and found to be more or less effective. These observations usually were not controlled and paid no attention to the fact that in many of the enumerated conditions it is possible to achieve similar results with other and often simpler forms of heating. The Council on Physical Therapy of the American Medical Association[1] has also issued a list of its own and regards all methods of diathermy as equally applicable. Generally speaking, inflammatory conditions of inner organs, bones, joints, and bursæ form the logical field of attack by penetrating heat methods—long wave and short wave diathermy.

In the light of seasoned observation long wave diathermy holds its own very definitely, although for a while the enthusiastic reports on the newer method seemed to have doomed the contact plate technique of long wave diathermy to oblivion and manufacturers in fact have discontinued the making of long wave apparatus. As to definite reports on comparative results obtained with the two methods, Delherm and Fischgold[7] believe that short wave diathermy in the main gives results similar to those with long wave diathermy; it is useful especially for regions in which it is difficult to apply diathermy. In gynecologic conditions Waters[36] reported on a series of 82 cases of chronic inflammation, Kovesligethy-Buben[16] on 500 patients with acute and subacute inflammation, and Otto[27] on 174 patients, 74 with acute and subacute pelvic inflammation and 100 chronic. These clinicians generally state as an advantage of short waves their applicability and efficiency in acute cases, whereas long wave diathermy is only indicated in chronic cases. The contention that short wave diathermy is preferable in acute cases and long wave diathermy in chronic cases can be explained by the fact that, with the original air-spaced technique, as a rule mild heating was applied which is well tolerated and beneficial in acute cases. Long wave diathermy with the contact-plate method results usually in more intense heating, better suited to chronic cases. It is

quite problematical whether early experimental findings indicating that heating by short wave diathermy is more intense in the depth have any practical clinical meaning, because in actual practice the heating effect depends on a number of factors, such as size and spacing of electrodes, strength of the current, and length of treatment.

Kovacs[15a] states that short wave diathermy as usually applied with large size electrodes or an inductance coil results in a spreading of its lines of force over all adjacent structures with considerable wasted energy. This must be considered in treating heat-sensitive patients and such locations as the head or the neck where unnecessary heating of non-affected parts is to be avoided. Long wave diathermy should be preferable in treating superficially located muscles and bursæ, many of the joints, and the cervical spine, because it allows better localized heating.

Schliephake[35] and many of his followers regard purulent infections of the skin, furuncles, carbuncles, paronychia, dental abscesses and lung abscesses as conditions in which short wave diathermy, especially of the shorter wave lengths, affords striking relief of pain and speedy resolution. This has been corroborated in the case of facial furuncles by such American observers as Egan,[9] Brugsch and Pratt[3] and Laszlo.[20] Experienced clinicians, on the other hand, have emphasized that in all suppurative processes mild heating is sedative and recall that in acute conditions there is a natural tendency toward fairly quick recovery. Radiant energy in the form of Roentgen rays has repeatedly been reported as of special value in promptly reducing inflammation and hastening healing in furuncles and carbuncles (Meyer[23] and others). Kovacs[15b] reported years ago that in localized skin infection exposure to luminous heat repeated several times a day gives very marked relief and satisfactory resolution. The late E. P. Cumberbatch[6] was able to achieve similar results with long wave diathermy carefully applied. Schliephake himself advises only mild doses of short wave diathermy. Hence, definite proof of the alleged specificity of short wave diathermy in these conditions will be brought about only by comparative observations on a large series of controlled cases. So far no one has presented such a study.

Short wave provocation as a diagnostic aid in focal infections was proposed by Gutzeit and Kuechlin[10] who found an increase of the sedimentation rate in a case of active dental infection after applying short wave diathermy to the site. Such findings were corroborated by Liebesny,[21] while Pfankuch and Karpf[30] state that the response is individual and does not permit any definite conclusions. Hence there appears to be need for controlled research here also.

Problems of Technique. In the practical application of short wave diathermy, new problems have arisen which so far have been only partly solved.

A definite drawback of the technique of short wave diathermy as employed up to the present time is the lack of dosage guidance except as supplied by the patient's sensation. This crude method of dosage estimation, in spite of the necessity of applying varying dosages in different pathologic conditions, has generally resulted in the hit or miss manner of application by neophytes. During the past two years reports

of the successful construction of "dosimeters" for short wave diathermy have been presented by Mittelmann,[24] Mittelmann and Kobak,[25] and Kowarschik.[17a] These dosimeters indicate the actual absorption of short wave energy. They have not yet stood the test of general clinical use; and, of course, they add to the expense of the apparatus.

Orificial treatment with short wave diathermy to the prostate, seminal vesicles and to the female pelvic organs has been troublesome because of the difficulty of proper electrode spacing and dosage measurement. In long wave diathermy with metal contact electrodes inserted in the rectum, vagina or cervix uteri, it is possible to estimate dosage fairly accurately even without a thermometer, by the reading of the milliammeter. The skin sensation under the dispersive electrode is also an aid for the experienced, if the same set-up is employed. In short wave diathermy, none of these considerations prevails and the only safe guide is a thermometer inserted into the shaft of the orificial electrode showing that the rise of temperature in its immediate vicinity is within the safe estimated tolerance. The selection of the best type of active electrode whether insulated or not and the spacing of the dispersive electrode is also a problem, as any one having attempted such treatment with the variety of apparatus available will know. In Europe, glass enclosed electrodes are used for vaginal treatments. In the United States, the advice generally given is to administer orificial treatments with metal electrodes and long wave apparatus or else to use the induction coil technique. It is doubtful, however, whether heating the soft tissues by a single coil *in toto* from the skin inward will accomplish the same result as the combination of an internal and an external electrode.

Metal direct contact plates with short wave diathermy as first reported on by Kovacs[15c] offer a solution to some of the difficulties of technique. Their use is made possible by the introduction of extra condensers into the patient circuit of the short wave apparatus, thus compensating for the loss of spacing. While it involves the return to direct contact plate technique with the necessity of careful adaptation of the metal plates, its practical advantages are: 1, it permits the use of a simple milliammeter in the patient circuit and a fairly accurate estimate of dosage; 2, the treatment cables no longer form part of the receiving circuit and can be handled without drawing energy from them and without the danger of their overheating; 3, finally, it obviates superfluous scattering of energy into surrounding tissues as well as into space and also cuts down radio interference considerably.

Radio interference by short wave apparatus has been the subject of a national conference[5] and has been amply discussed by Williams,[37] Krusen[18] and others. Short wave diathermy causes interference in important short wave radio communications on land, and sea and also in television. With high powered apparatus and excess radiation into space this interference may extend hundreds of miles away from the apparatus. Any of the several remedies suggested—such as shielding the apparatus, installing "crystal control," use of only a certain frequency or wave length or to operate the apparatus only at certain hours—would add greatly to the cost of equipment or necessitate scrapping much of the existing equipment or restrict its extent of

usefulness. This matter is now subject to serious consideration as regards Federal control, and the medical profession is on the defensive to protect its legitimate interest, which antedates the advent of radio.

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RADIOLOGY

UNDER THE CHARGE OF

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THE STOMACH.

THE stomach is an organ that is static and immutable but with an integrated and highly complex mechanism which must adjust itself continuously to the forces in its environment, both external and internal. Meteorologic forces such as changes in temperature, humidity, barometric pressure and the intensity of light are the most constant to which the individual must adjust himself. Dietetic factors such as lack of

intake or loss of certain vitamins or minerals play an important part as factors of gastric disorders. An individual who may be depleted of certain substances or changed chemically by other factors will react emotionally differently from another individual who is well buffered in his chemical and constitutional make-up. Emotional disturbances play an important part in producing both psychic and physical disturbances.

Drawing attention to these facts, Laing[1] discussed the clinical aspects of disorders of the stomach.

One of the disturbing features in the roentgenologic examination of the gastro-intestinal tract from the standpoint of the referring physician is the frequency with which the findings are negative. Over a period of years, in more than 70% of a group of cases in which the histories were carefully analyzed and the patients were sent for roentgenologic examination of the stomach at the Mayo Clinic because of suggestive symptoms, the findings were not positive. In somewhat more than 50% of the cases in which the findings were positive the lesions did not actually involve the stomach but were ulcers of the duodenum. Less than 15% of all patients examined, therefore, had lesions of the stomach itself to account for their symptoms.

Of the group of cases in which the roentgenologic findings were negative, operation was performed in approximately 5% in each year; in the great majority of cases the operation was performed for some other type of disorder and there was an opportunity to examine the stomach, at least by manual palpation, and no lesion involving the stomach was found. Of duodenal ulcers found at operation less than 2% in any year failed to produce roentgenologic findings. Of gastric ulcers found at operation less than 1.5% failed to produce roentgenologic findings. In the cases in which carcinoma of the stomach was found at operation, negative roentgenologic findings were obtained in less than 2% of the cases each year.

The ratio of the occurrence of duodenal ulcer, gastric ulcer and carcinoma of the stomach was 80 to 5 to 15 in that order. Organic lesions of the stomach, therefore, were found in approximately 20% of the cases in which the roentgenologic findings were positive. Of the organic lesions 15% were carcinomas; a small number of these involved the esophagus and some others involved the lower part of the esophagus and the cardiac end of the stomach.

Laing pointed out that the stomach of the intact human being is rather inaccessible and studies under normal and abnormal conditions are chiefly by indirect methods. In general, the methods of study were limited to: 1, the correlation of clinical symptoms with the pathologic findings so well brought out in about 1830 by Cruveilhier; 2, direct observation during surgical operations; 3, direct observation of the pylorus through gastric stomas such as made by Beaumont more than 100 years ago and recently by Carlson; 4, visualization of the stomach by means of Roentgen rays, following various procedures such as the giving of certain foods and drugs and noting their effects; 5, gastroscopic examination.

Laing felt that the symptom complex called "pylorospasm" merited much more consideration than it had received in the past. He defined pylorospasm as a spastic contraction of the thickened circular muscle

coat known as the pyloric sphincter, which at times produces various gastric disturbances.

In the roentgenoscopic examination of the stomach, pylorospasm may be a potential of considerable difficulty. It may simulate closely the roentgenoscopic image of carcinomatous involvement of the pyloric end of the stomach. To the experienced observer, it will suggest the presence of an ulcer, usually on the lesser curvature at some distance above the pylorus, and direct a careful search for further evidence in the way of a niche on the lesser curvature or the frequently accompanying incisura on the greater curvature side.

Laing stated that the etiologic factors in pylorospasm may be intrinsic or extrinsic. The most common intrinsic factor is a peptic ulcer of the stomach or duodenum. Under extrinsic causes he listed reflex factors due to organic lesions outside of the stomach. The reflex disturbance due to cholecystic disease is particularly interesting. Gall stones, which in themselves are producing no localizing symptoms, might be the basis for a so-called indigestion picture. It is commonly held that gall stones may remain for a period of years in the gall bladder without producing any symptoms. If a careful history is taken in all cases it will be found that patients with gall stones often have had attacks of so-called acid stomach or indigestion. Pylorospasm, in his experience, may be produced by a slight change in position of the stones. According to Laing, waiting for severe pains in such cases before instituting surgical investigation and removing the stones does not seem, in the face of clinical evidence, to be warranted.

Appendicitis is another important cause of pylorospasm. Reflex symptoms resulting from functional disturbances in other organs, such as the so-called irritable colon, are factors in causing pylorospasm. Laing quoted Smith and his co-workers as assured that the localized epigastric distress commonly associated with irritability of the colon is gastric in origin and is brought about by reflex stimulation of the stomach. Such findings agree with the observation of Carlson on animals, namely, that sufficient stimulation of all sensory visceral nerves may produce a contraction of the pylorus. Clinically, Laing wondered if the particular organ or structure having the lowest threshold is the one which produces the symptoms. Biliary dyskinesia (impairment of the power of voluntary movement) is another symptom complex which might be explained in the same manner.

Under systemic causes of pylorospasm, Laing listed the factors to which one must look for explanation of a considerable group of conditions in which the findings of the roentgenologic examination are negative in the face of a history of definite "indigestion." These factors are as follows:

1. Allergic states brought about by the ingestion of some of the more common offenders, as milk, eggs, and shell fish, to which the particular individual is sensitive. The gastro-intestinal manifestations have a marked similarity to those noted in bronchial asthma, namely, spasm of smooth muscle and edema of the mucous membrane. 2. Toxic states caused by the excessive use of tobacco. 3. Endocrine disturbances. Symptoms of dysfunction as manifested at the time of menstruation and the menopause are commonplace. The signs and symptoms associated with the neuromuscular imbalance in both hyperthyroid

and hypothyroid states often are encountered. 4. Diseases of the central nervous system such as locomotor ataxia may be an occasional cause. Gastric crises examined roentgenologically during an attack may show nothing but a pylorospasm. An organic lesion of the brain, such as a tumor, may be another productive agent. Psychoneurosis as a cause of pylorospasm occurs with much greater frequency than is at present suspected. If the spasm is of short duration in any of these conditions there may be no dilatation of the stomach, but if the spasm is persistent and prolonged, a dilatation may occur owing to the associated hyperperistalsis and hypersecretion.

An understanding of the mode of production of the patient's subjective symptoms and the way in which they may be modified by his environments, together with the taking of a careful history, is of great importance to the clinician and to the roentgenologist. There may be nothing abnormal noted on physical examination even in the presence of either a functional or an organic disturbance of the gastro-intestinal tract.

If organic changes are present, by roentgenologic examination the exact position and nature of the pathologic process are defined. If surgical measures are indicated they can be carried out at an early date, allowing a distinct advantage in prognosis. Whether surgical intervention is or is not indicated, subsequent examinations can be made in order to follow the results of therapy in selected cases.

Laing drew attention to the seasonal incidence of the symptoms in cases of peptic ulcer. Moynihan, he stated, emphasized this many years ago and stressed the constitutional type of individual in whom it occurred; Einhorn also was credited with stressing this fact and bringing out that in the majority of his cases the symptoms occurred in the spring and fall. During these seasons there is a greater variability of the meteorologic environment. This factor must play an important part in the reaction of the unstable individual who is afflicted with an ulcer. Laing quoted Preuner as finding that climatic conditions had a similar effect on asthma in his experimental work on guinea-pigs. Preuner found that the induced asthma was not dependent on such meteorologic factors as temperature, humidity or atmospheric pressure as long as these factors remained constant, but that during periods of rapid change in climatic conditions the average severity could be increased about 50%. This new field of experimental meteorobiology may conceivably assume an important place in future gastro-intestinal and other studies.

Seasonal variations in the concentration of calcium, phosphorus and vitamin G in the blood occur. The iodine content of the thyroid gland in animals has been shown to vary markedly with the seasons. Clinically, other diseases and symptom complexes exhibiting periodicity are those of the skin, prostate gland, and certain types of asthma and hay fever, sinusitis, and shoemaker's tetany. Peterson and de Takats, Laing stated, have shown that pulmonary emboli are predominantly seasonal in their occurrence. Ulcers have been produced experimentally in the stomachs of dogs by the use of pitressin, in the exact situation in which they occur clinically in human beings. The blood supply to the tissue was diminished through increased tone or actual spasm of both muscle and blood-vessels, with subsequent digestion of the involved region and an ulcer thereby produced.

Laing's article was one of a series in a symposium on organic and functional disorders of the stomach. In the list of methods of examining the stomach he included gastroscopic examination. Although he stated that time did not permit full discussion of the subject, he furnished much food for thought to be applied to the study of the factors concerned in the production of functional gastric disorders. As heretofore stated, functional disorders must be responsible for the symptoms in the greater number of the approximately 70% of cases in which roentgenologic findings are negative. This group of patients is being more and more frequently subjected to gastroscopic examination. Where there has been opportunity to compare the results of roentgenologic examination and gastroscopic examination it was found that approximately 45% of the stomachs showing negative findings at roentgenologic examination showed some type of mucosal change at gastroscopic examination. This varied from changes which were interpreted as traumatic changes resulting from instrumentation in a few cases to frank alterations in the form of the gastric rugæ or definite changes from what has been recognized as the normal condition of the gastric mucosa. Organic lesions not elicited on roentgenologic examination were reported on gastroscopic examination in only 2.59% of the cases in this group; 2.3% gastric ulcers and 0.29% of carcinomas.

These facts would seem to indicate that there is a large group of cases of functional disorders of the stomach in which there is a definite field for the application of the knowledge compiled by Laing and that the means of recognizing these disorders are available in gastroscopic examination.

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REFERENCE.

(1.) **Laing, G. H.**: Am. J. Roentgenol., **43**, 805, 1940.

Correction.—The price of Dr. Roesler's "Atlas of Cardioroentgenology" is $8.50 and not $12.50, as stated in our October issue (p. 547).

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